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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

DECEMBER, 1913

ORIGINAL ARTICLES

THE PATHOLOGY OF THE THYROID GLAND IN EXOPHTHALMIC GOITER.[1]

By Louis B. Wilson, M.D.,

DIRECTOR OF LABORATORIES, MAYO CLINIC, ROCHESTER, MINNESOTA.

The studies on which the present paper is based are a continuation of those first reported to the Association of American Physicians five years ago.[2] At that time, I gave a detailed analysis of the pathological examination of 259 thyroids, removed from patients listed as "exophthalmic goiter" in the Mayo Clinic from January 1, 1905, to May 10, 1908, and in addition a review of the pathological reports on 35 cases similarly listed in the Mayo Clinic prior to January 1, 1905. While these cases were not all such as we would now diagnosticate exophthalmic goiter, they were all toxic, and probably contained as high a percentage of cases of true exophthalmic goiter as could have been found in any clinical list at that time.

The solution of problems of the pathology of the thyroid has long been rendered more difficult by indefinite clinical diagnoses and nomenclature, and this no doubt accounts for much of the disagreement between workers in different clinics. While nontoxic cases usually have been diagnosticated clinically "simple goiter," and cases with marked symptoms have been diagnosticated "exophthalmic goiter," yet many cases with mild symptoms have also been called "simple goiter," and many cases, though not

[1] Presented before the Association of American Physicians, Washington, D. C., May 7, 1913.

[2] Wilson, Amer. Jour. Med. Sci., 1908, cxxxvi, 588 to 605.

true exophthalmic, yet markedly toxic, have been called by most clinicians "exophthalmic goiter."

Though a sharp distinction between the two clinical types of toxic cases—exophthalmic and non-exophthalmic—had not been made in 1908, I was able to show that pathologically there were two distinct types of glands to be found among thyroids removed from toxic goiter cases. While purposely avoiding as much as possible previously used technical terms, I attempted to simplify our conception of the pathology by pointing out that the essential element in a large percentage of the cases was an increase in the amount of working tissue—parenchyma cells—within the previously formed acini, or, in other words, hypertrophies, hyperplasias, and regenerations, while in a smaller percentage of the cases there was an apparent increase in the amount of working tissue—parenchyma—due to an increase in the number of acini, or, in other words, adenomas, adenomatoses, etc. Class I, containing the hypertrophies, hyperplasias, and extreme regenerations, constituted 79 per cent. of the total number of specimens examined, while Class II, containing the fetal and colloid adenomas, the adenomatoses and the so-called simple colloid thyroids, constituted 21 per cent. of the specimens examined.

In comparing my theoretical estimate of the stage and severity of the disease as indicated by the above data with the clinical facts as previously observed and noted by Plummer, it was shown that a direct relationship existed between the apparent functional activity of the gland and the stage and severity of the clinical symptoms. In reviewing the clinical data of his more recent cases, Plummer[3] has found that practically all, if not all, of the cases of clinically true exophthalmic goiter lie in the pathological groups showing hypertrophy and hyperplasia, while the toxic non-exophthalmic cases are scattered among the other pathological groups. We have, however, up to the present time, continued the ordinary method of listing clinically all severe toxic goiter cases closely resembling exophthalmic cases[4] on the "exophthalmic goiter" list, while on the "simple goiter" list are placed those cases in which there are slight or no acute toxic symptoms. Our "exophthalmic goiter" list therefore contains those cases coming to our clinic which are ordinarily diagnosticated exophthalmic goiter, but which Dr. Plummer divides clinically into two classes, exophthalmic toxic, and severe non-exophthalmic (*i. e.*, non-hyperplastic) toxic.

I have recently reviewed all the gross and microscopic fixed tissue at hand from the cases reported in 1908, and, in addition, have studied grossly and microscopically in fixed tissues all the glands available which have been removed between May 10, 1908, the date of my previous report, and January 1, 1913, from all patients

[3] Amer. Jour. Med. Sci., 1913, cxlvi, 790.

[4] Plummer, loc. cit.

Indicate amount of gland involved by common fraction. Describe all encapsulated tumors in *red* in the

	Identification Data					
	Office No.	Hospital No.	Name	Address	Sex	Age
1						
2						

Microscopic Indicate amount of gland involved by common fraction. Describe all encapsulated tumors in *red* in th

	Vessels		Stroma			Acini				
	Size of Smaller Bloodvessels 1. Diminished 2. Normal 3. Increased 4. Dilated	Size of Smaller Lymphatics 1. Diminished 2. Normal 3. Increased 4. Dilated	Amount in Walls of Acini 1. Reduced 2. Normal 3. Increased 4. Great Increase	Inflammatory Changes 0, 1, 2, 3, 4	Degeneration H-Hyaline Ct-Cartilage M-Myxomatous Cl-Calcareous 0, 1, 2, 3, 4	Size of Cavity 0-None 1-Small 2-Medium 3-Large 4-V. Large	Shape T-Tubular lumenless S-Spherical lumenless N-Spherical lumen Normal I-Irregular P-Papillæ 1, 2, 3, 4	Microcysts (Distended Single or Joined Acini) Size 0, 1, 2, 3, 4	Size 0-Embryonic 1-Atrophy 2-Normal 3-Hypertrophy 4-Very Marked Hypertrophy	Numbe 1. Reduce 2. Normal 3. Hyperp 4. Marked Hyper-plasi
1										
2										

TABLE I

EXOPHTHALMIC GOITER, PAGE 60 A, YEAR 1912

in *red* in the upper part of the case space, and all other tissues in black in the lower part. MACROSCOPIC

		OPERATIONS				DIAGNOSIS
Age	Weight Kilos Height Centimeters	First Date and Character	Second Date and Character	Third Date and Character	Amount of each lobe removed R-Rt. L-Lt. I-Isth.	Immediate with corrections in red

.....GOITER, PAGE.....B, YEAR.....

s in *red* in the upper part of the case space, and all other tissues in black in the lower part.

	PARENCHYMA CELLS							SECRETION		
	Number 1. Reduced 2. Normal 3. Hyperplasia 4. Marked Hyperplasia	Shape S-Sperical (Embryo.) Cb-Cuboid (Normal) Cl-Columnar (Hypertrophy) F-Flattened (Pressure) 1, 2, 3, 4	Cytoplasm Cl-Clear G-Granular V-Vacuolated Cd-Colloid 1, 2, 3, 4	Nucleus size of 1. Shrunken 2. Normal 3. Swollen 4. Fragmented	Nucleus staining Reaction 1. Feeble 2. Normal 3. Intense 4. Irregular	Mitosis 0, 1, 2, 3, 4	Cytolysis 0, 1, 2, 3, 4	Amount 0, 1, 2, 3, 4	Density of Staining Reaction 0-No Stain 1-Feeble 2-Moderate 3-Marked 4-Intense	Granular Contents A-Amorphous C-Crystalline E-Epithelium 0, 1, 2, 3, 4

TABLE I

EXOPHTHALMIC GOITER, PAGE 60 A, YEAR 1912

r tissues in black in the lower part. MACROSCOPIC

OPERATIONS			DIAGNOSIS	WEIGHTS IN GRAMS			
Second Date and Character	Third Date and Character	Amount of each lobe removed R-Rt. L-Lt. I-Isth.	Immediate with corrections in red	Total of all tissue removed	Encapsulated Tumors	Removed Gland Tissue outside of encapsulated Tumors	Entire Gland Estimated weight outside encapsulated Tumors

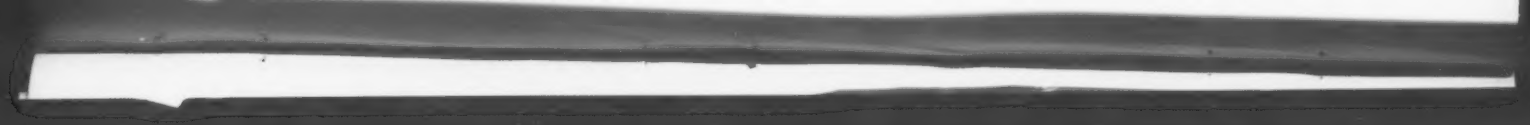
.....GOITER, PAGE.....B, YEAR.....

er tissues in black in the lower part.

				SECRETION			DIAGNOSIS FINAL PATH.		CHEMISTRY			
Nucleus staining Reaction 1. Feeble 2. Normal 3. Intense 4. Irregular	Mitosis 0, 1, 2, 3, 4	Cytolysis 0, 1, 2, 3, 4	Amount 0, 1, 2, 3, 4	Density of Staining Reaction 0-No Stain 1-Feeble 2-Moderate 3-Marked 4-Intense	Granular Contents A-Amorphous C-Crystalline E-Epithelium 0, 1, 2, 3, 4	Histology	Class	Amount of Iodine per Gram of Dry Gland	Acetonitril Reaction of Gland Tissue	Acetonitril Reaction in Blood	Pa

	General Characteristics								
Entire Gland Estimated weight outside encapsulated Tumors	Consistency 1.-Very Soft 2.-Soft 3.-Firm 4.-Hard	Roughness of Outer Surface 0-Smooth 1. 2. 3. 4.	Capsule 0-V. Thin 1-Thin 2-Medium 3-Thick 4-V. Thick	Hemorrhage 0. 1. 2. 3. 4.	Degeneration H-Hyaline Ct-Cartilage Mx-Myxomatous Cl-Calcareous 0, 1, 2, 3, 4	Cyst Size of 0-None 1-Small 2-Medium 3-Large 4-V. Large	Bloodvessels Size of Larger 1. 2. 3. 4.		
									1
									2

	Summary				Diagnosis of Clinical Condition			Prognosis	Office No.	
stomtril section in Blood	Index of Total Parenchyma per Kilo Body-weight	Index of Total Function	Index of Excretion	Index of Total Circulating Secretion	Stage of Toxic Symptoms 0, 1, 2, 3, 4	Severity of Toxic Symptoms 0, 1, 2, 3, 4	Severity of Second-ary Changes 0, 1, 2, 3, 4	RT-Relief of Toxic Symptoms 0, 1, 2, 3, 4 RS-Relief of Secondary Symptoms 0, 1, 2, 3, 4		
										1
										2



on our "exophthalmic goiter" list. This includes a total of 1208 thyroids from patients all of whom had shown marked toxic symptoms, though not all of whom, in the light of our present clinical knowledge, would now be diagnosticated true exophthalmic goiter. In addition to these 1208 glands from toxic cases, I have similarly studied the glands removed during the year 1912 from cases grouped clinically as "simple goiters," 585 in all. These latter 585 thyroids are from patients presenting very slight or no acute toxic symptoms. I have further studied the thyroids from a number of human embryos and from children, adolescents, and adults coming to autopsy without clinical history of thyroid derangement. My observations on the latter groups will be presented in later papers.

In order to maintain a standard of comparison in the analyses of these cases, it has been found necessary to adopt numerical equivalents for amount, size, degree, etc., and the analytical data thus designated has been tabulated on forms parallel in size and arrangement of names with those used by Plummer for the tabulation of the clinical data. The headings of the tables are shown in Table I.

All pathological observations have been made wholly independently of the clinical observations and not compared with the latter until the entire series was completed.

While many thyroids may each present a great variety of histological pictures, yet a careful examination of a large number of sections from blocks of fixed tissue from different areas combined with the examination of the gross specimens permits one to classify the glands with considerable definiteness. In grouping the specimens, I have classified them with but slight change on the basis which I adopted in 1908 and elaborated last year.[5] Thus groups A, B, C, and D represent Class I, namely; the parenchymatous hypertrophies and hyperplasias and extreme regenerations, while groups E, F, G, and H represent Class II, namely, the "adenomas," "adenomatoses," and "colloid goiters."

Hypertrophy and hyperplasia are almost always intermingled, but it is possible to subdivide the hypertrophies and hyperplasias into three classes: Group A, early primary parenchymatous hypertrophy and hyperplasia (see Fig. 1); Group B, active advanced primary parenchymatous hypertrophy and hyperplasia (see Fig. 2); Group C, regressing primary parenchymatous hypertrophy and hyperplasia (see Fig. 3). I have used the term "primary" in each of these classifications because I believe it represents a stage of hypertrophy and hyperplasia developing in parenchyma which previously has not been markedly atrophic. Group D contains those specimens in which a marked regeneration of parenchyma is found developing on apparently previously atrophic parenchyma

[5] Wilson, Northwest Medicine, Seattle, Washington, 1913, v, 1 to 5.

lining the walls of previously distended, colloid-filled acini (see Fig. 4). This regeneration is marked by the presence of numerous minute acini lined with low spherical or cuboidal epithelium and filled quite early with densely staining colloid. Critically con-

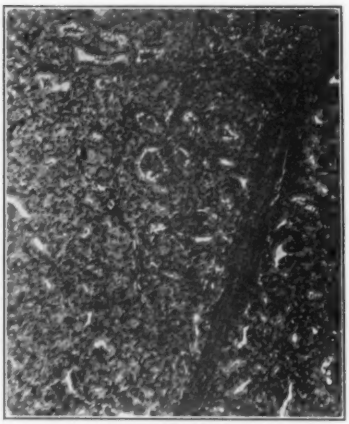


FIG. 1.—Photomicrograph of a section of thyroid. × 120. Type A. Early primary parenchymatous hypertrophy and hyperplasia. From a case of clinically early true exophthalmic goiter.

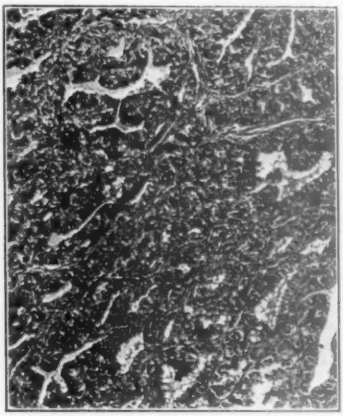


FIG. 2.—Photomicrograph of a section of thyroid. × 120. Type B. Advanced primary parenchymatous hypertrophy and hyperplasia. From a case of clinically severe true exophthalmic goiter.

FIG. 3.—Photomicrograph of a section of thyroid. × 120. Type C. Regressing primary parenchymatous hypertrophy and hyperplasia. From a case of clinically true exophthalmic goiter, late stage.

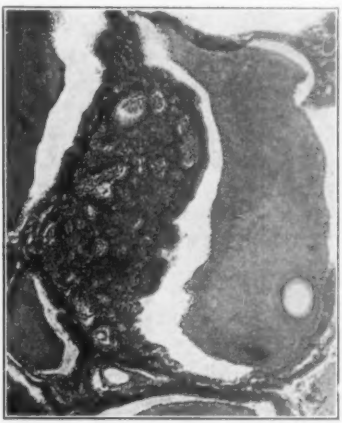


FIG. 4.—Photomicrograph of a section of thyroid. × 120. Type D. Secondary regeneration of atrophic parenchyma. From a case of clinically toxic non-exophthalmic goiter.

sidered, the process is really a form of hyperplasia, and it is possible indeed for it to progressively grade over into primary hypertrophy and hyperplasia, but I have rigidly excluded from groups A, B, and C all glands which did not show marked infolding of acinar walls

FIG. 5.—Photomicrograph of a section of thyroid. × 120. Type E. Fetal adenoma. From a case of clinically toxic non-exophthalmic goiter.

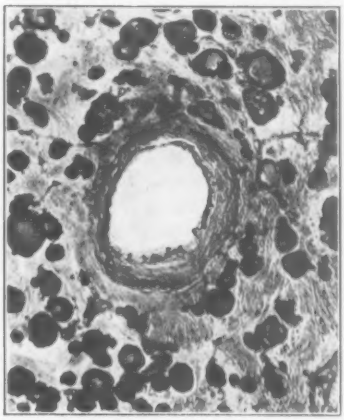


FIG. 6.—Photomicrograph of a section of thyroid. × 120. Type F. Degenerating fetal adenoma. From a case of clinically toxic non-exophthalmic goiter.

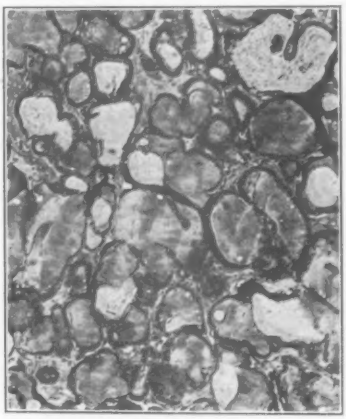


FIG. 7.—Photomicrograph of a section of thyroid. × 120. Type G. Adult, "colloid" adenoma. From a case of clinically toxic non-exophthalmic goiter.

FIG. 8.—Photomicrograph of a section of thyroid. × 120. Type H. "Colloid thyroid." From a case of clinically non-toxic goiter.

lined with columnar epithelium. On the other hand, it is frequently impossible to draw the line between those degrees of regeneration in a colloid thyroid which might fairly be presumed to be the cause of toxic symptoms and those in which no effect can be noted. All that I have attempted here is to note in a study of the glands removed from known toxic cases the presence or absence of marked regeneration. While theoretically it would seem to be extremely confusing to differentiate secondary regenerations from primary hypertrophies and hyperplasias, yet, as a matter of fact, when sections from material which has been properly fixed and stained are studied, the task is not a difficult one.

Of the groups in Class II, group E contains the actively growing, non-degenerating fetal adenomas (see Fig. 5); group F contains fetal adenomas which show any of the several types of degeneration —myxomatous, hyaline, calcareous, etc. (see Fig. 6); group G contains those definitely encapsulated adenomas whose acini are too large to be classified as fetal and which may or may not be degenerated (see Fig. 7); and group H contains those thyroids not included in the previous classes, many of which, though not presenting definitely encapsulated tumors, yet are composed of more or less segregated groups of acini presenting a picture which, following Adami's lead, I prefer to class as "adenomatoses" (see Fig. 8).

The accompanying table gives the classification of the thyroids studied according to the above grouping.

A study of the table reveals the following interesting points:

1. Approximately four-fifths, 79 per cent., of all thyroids from patients who had exhibited sufficiently severe acute toxic symptoms to warrant the clinician in placing them on the "exophthalmic goiter" list, showed marked hypertrophy or hyperplasia, or, more usually, both.

2. During the year 1912 this percentage arose to 89. At the same time, a parallel examination by the same observer of 585 thyroids from patients on the "simple goiter" list for 1912 showed but four cases—less than 1 per cent.—with hypertrophy and hyperplasia. Of these four cases, three were children and one was a young adult female whose lack of toxic symptoms can be accounted for only on the hypothesis that she was highly resistant and had not yet had time to be affected.

3. During the years 1911 and 1912 every patient diagnosticated clinically as true exophthalmic goitre and on whom thyroidectomy was done, furnished thyroid tissue which pathologically was placed in the groups marked A, B, or C, that is, showing primary parenchymatous hypertrophy and hyperplasia.

4. So far as can be determined none of the 133 patients—11 per cent.—whose thyroids showed only secondary regeneration of atrophic parenchyma would now be classified clinically according

to Plummer as true exophthalmic goiter. This distinction is clinically sharp and positive for the years 1910, 1911, and 1912, and not yet critically reviewed from the clinical standpoint for the preceding years.

5. The statement in paragraph 4 is equally true for the 130 cases—10 per cent.—whose thyroids are grouped as E, F, G, or H (adenomas, etc.).

6. At the same time these groups D, E, F, G, and H—regenerations, adenomas, colloids, etc.—contain 97 per cent. of all thyroids removed from patients on the "simple goiter" list for 1912.

TABLE II.—PATHOLOGICAL CLASSIFICATION OF THYROIDS FROM PATIENTS ON "EXOPHTHALMIC GOITER" LIST FROM JANUARY 1, 1905, TO JANUARY 1, 1913, AND OF THYROIDS FROM PATIENTS ON "SIMPLE GOITER" LIST FOR 1912.

		"Exophthalmic Goiter" List.									"Simple Goiter" List.	
	Years . . .	1905	1906	1907	1908	1909	1910	1911	1912	Totals	1912	
A	Early primary parenchymatous hypertrophy and hyperplasia.	...	1	4	2	1	3	15	6	32 3%	..	A
B	Advanced primary parenchymatous hypertrophy and hyperplasia.	4	26	35	41	44	68	108	89	415 34%	1	B
C	Regressing primary parenchymatous hypertrophy and hyperplasia.	7	21	44	55	46	78	107	140	498 41%	3	C
	Total hypertrophy and hyperplasia (A + B + C).	11 69%	48 83%	83 68%	98 69%	91 71%	149 77%	230 81%	235 89%	945 79%	4	
D	Secondary regeneration of atrophic parenchyma of "colloid" goiter.	1 6%	3 5%	24 20%	24 17%	17 13%	30 15%	20 7%	14 5%	133 11%	50 9%	D
E	Fetal adenomas.	1	3	7	17	8	2	12	2	52 4%	35	E
F	Degenerating fetal adenomas.	3	3	5	3	5	12	21	10	62 5%	101	F
G	Adult ("colloid") adenomas.	...	1	1	...	6	1	...	3	12 1%	128	G
	Total adenomas (E + F + G).	4 25%	7 15%	13 11%	20 14%	19 15%	15 7%	33 12%	15 6%	126 10%	264 44 %	
H	Atrophic parenchyma ("colloid") thyroids, "adenomatoses," etc.	...	...	1	...	1	2	...	...	4	259 44 %	H
	Malignant tumors.	...	...	...	...	...	...	...	...	..	8 1½%	
	Total number of thyroids	16	58	121	142	128	196	283	264	1208	585	

In attempting to estimate from the pathological data alone the stage of the toxic clinical symptoms, the following factors have been taken into account: (1) Age of the patient, (2) weight of the portion of gland removed, (3) character of the bloodvessels, (4) amount of stroma, (5) size and shape of the acini, (6) amount of hypertrophy and hyperplasia of the parenchyma cells, and (7) amount and density of the secretion contained within the acini. These factors

must all be considered in estimating the product and output of the gland so far as may be made from a pathological examination of the tissues. A careful consideration of all these factors has been made in each case examined and a tentative estimate given of the stage and severity of the disease at the time the patient was operated on. These estimates have been compared in parallel columns with the clinical estimates made by the examining physician for all cases operated on during 1910, 1911, and 1912 (the only years for which the full clinical data, except of those given in my paper of 1908, have as yet been critically reviewed). The results may be briefly summarized as follows:

1. Of the 24 cases diagnosticated pathologically as Group A (early primary parenchymatous hypertrophy and hyperplasia), 21 (87.5 per cent.) had exhibited symptoms for but three months or less.

2. Of the 265 cases placed pathologically in Group B (advanced primary parenchymatous hypertrophy and hyperplasia), 11 (4 per cent.) gave a history of toxic symptoms for but three months, 155 (58 per cent.) from three months to one year, 34 (13 per cent.) (almost all young individuals) slightly over a year, but with a ligation shortly preceding thyroidectomy, while 65 (24.5 per cent.), these again almost all young individuals, had exhibited symptoms for over a year and had had no ligation previous to thyroidectomy.

3. Of the 325 cases diagnosticated pathologically as group C (regressing primary parenchymatous hypertrophy and hyperplasia), 8 (2 per cent.) gave a history of but three months' duration of symptoms (and without ligation prior to thyroidectomy), 25 (8 per cent.) gave a history of one year or less duration of symptoms (and without ligation prior to thyroidectomy), while the remainder, 292 (90 per cent.), gave clinical histories of more than one year's duration or had had a ligation some weeks before the performance of thyroidectomy.

Thus it will be seen that notwithstanding the inaccuracies of patients' statements as to the duration of symptoms, notwithstanding the confusing factor of a ligation previous to thyroidectomy, and notwithstanding the difficulties of correctly estimating the total function from an anatomical study of but a portion of a gland, the fact remains that the stage of true exophthalmic goiter can be estimated with considerable accuracy from the pathological data alone in about 80 per cent. of all cases examined.

In attempting to estimate the severity of the toxic symptoms in the cases with true exophthalmic goiter, all of which had shown pathologically some stage of hypertrophy and hyperplasia in the thyroid (Groups A, B, or C), the same factors were taken into consideration as those entering into the estimate of the stage of the disease. A careful consideration of these data resulted in the classification of the cases for 1910, 1911, and 1912 into the four

grades of severity: (1) Very mild, (2) moderate, (3) severe, (4) very severe. On only 542 cases out of the 614 was it possible to make a definite comparison of the estimated severity from the pathological standpoint with the severity as noted by the clinician just prior to thyroidectomy.

Out of these 542 cases, 29 were estimated pathologically as "1," or of "mild" severity. Twenty-two out of the 29 had been previously similarly grouped by the clinicain, or, in other words, the pathological estimate agreed with the clinical findings in 76 per cent. of the cases in this group.

Of the 306 cases estimated pathologically as "2," or of "moderate" severity, 235 were similarly placed by the clinician, an agreement of 77 per cent. in this group.

Of the 166 cases estimated as of severity "3," that is "severe," 117 were similarly grouped by the clinician, an agreement of 70 per cent.

Of the 41 cases estimated pathologically as severity "4," that is "very severe," 33 have been similarly grouped by the clinician, an agreement of 80 per cent.

Thus of the 542 cases on which the degree of severity was estimated from the examination of pathological specimens, such estimate agreed with the clinical estimate in 407 cases, or a total pathological accuracy of 75 per cent.

Conclusions. 1. A detailed pathological study of fixed tissue preparations from 1208 thyroids, removed from patients whose condition would ordinarily have been diagnosticated exophthalmic goiter, showed that 79 per cent. of the thyroids contained large areas of marked primary hypertrophy and hyperplasia. A parallel clinical study has shown that for a period of three years all cases with true exophthalmic goiter, and from whom gland tissue was removed, fall into this list.

2. In the above series of 1208 so-called "exophthalmic goiters" plus 585 so-called "simple goiters," or a total of 1793 thyroids, but 4 instances of marked primary hypertrophy and hyperplasia of the parenchyma have been noted in cases which did not show clinical symptoms of true exophthalmic goiter. Three of these four patients were children.

3. Twenty-one per cent. of the 1208 glands studied were either regenerations or adenomas. Clinically, while all of these were markedly toxic, all were chronic and none of them would now be grouped clinically as true exophthalmic goiter.

4. By assuming that the symptoms of true exophthalmic goiter are the results of an excretion from the thyroid, and by attempting to determine the amount of such excretion from the pathological data, one is able to estimate in a large series of cases the clinical stage of the disease with about 80 per cent. of accuracy

and the clinical severity of the disease with about 75 per cent. of accuracy.

5. It would therefore appear that the relationship of primary hypertrophy and hyperplasia of the parenchyma of the thyroid to true exophthalmic goiter is as direct and as constant as is primary inflammation of the kidney to the symptoms of true Bright's disease. Any considerable finding to the contrary I believe to indicate either inaccurate or incomplete observations on the part of the pathologist or clinician, or both.

THE CLINICAL AND PATHOLOGICAL RELATIONSHIP OF SIMPLE AND EXOPHTHALMIC GOITER.[1]

By H. S. Plummer, M.D.,

MAYO CLINIC,
ROCHESTER, MINNESOTA.

Up to January 1, 1909, 1004 operations had been done on 966 cases of goiter at St. Mary's Hospital. A brief review shows that we were classifying the cases as simple and exophthalmic goiter. We recognized that a considerable percentage of cases of so-called simple goiter had constitutional symptoms. Whether or not the cases having constitutional symptoms were placed on the simple or exophthalmic list depended upon how closely the clinical complex approached the well-known picture of Graves' disease.

Wilson, in 1908, after reviewing the available pathological material from the cases that had been diagnosed exophthalmic goiter, pointed out that 80 per cent. of the glands showed hyperplastic changes, and that in general the length and severity of the case history could be pointed out from the pathological findings. While it was impossible to overlook the fact that the tissue removed from the majority of patients having a well-developed picture of Graves' disease was hyperplastic, we could not come definitely to the conclusion that this evidence of activity on the part of the thyroid was a constant finding in exophthalmic goiter as long as 20 per cent. of the cases so diagnosed did not show this change in the thyroid.

At about this time a review of the clinical histories and pathological findings of the entire series listed as simple and exophthalmic goiters led to the following tentative conclusions: (1) that at least two distinct but similar types of thyroid intoxication exist one associated with non-hyperplastic goiter, the other with hyperplastic or hypertrophic thyroid; (2) that exophthalmos

[1] Read before the Congress of American Physicians, Washington, May 6, 1913.

should be noted only in cases having hyperplastic or hypertrophic thyroids; (3) that the failure of our statistics to show the above conclusions was due largely to the following errors: (*a*) accepting the clincial findings and diagnosis of exophthalmic goiter for all cases placed on the exophthalmic goiter list; (*b*) accepting the pathological findings from only a portion of one lobe of the thyroid; (4) that the clincial errors were attributing the tremor, tachycardia, etc., of neurasthenia, cardiovascular and nephritic diseases to the thyroid and noting the existence of exophthalmos when only a Stellwag's sign and naturally prominent eyes are associated with the thyrotoxicosis of non-hyperplastic goiter.

I have from time to time pointed out in discussions, statistical data bearing out the above conclusions, but have refrained from publication until going into a wealth of confusing detail to explain the apparent exceptions is unnecessary.

In writing the histories of the 3207 cases that have come to operation since January 1, 1909, forms were used covering the points which might later prove of interest. Figures and signs having, insofar as possible fixed values, were used in place of descriptive adjectives. Observations of facts and opinions were carefully distinguished. The clinical and pathological findings were placed in parallel columns without any comparison of notes on the part of the clinicians and pathologists. This made possible the compilation of statistics by clerks who were not in any way warped by preconceived ideas or a knowledge of factors other than those under immediate consideration.

The term thyrotoxicosis is here applied to the constitutional state associated with goiter. As a matter of convenience for quickly presenting the association of the clinical and pathological findings, the constitutional symptoms accompanying goiter were attributed to a toxemia, the result of a disturbed thyroid function. As a temporary expedient the cases were classified pathologically as hyperplastic and non-hyperplastic, and clinically as hyperplastictoxic, hyperplastic atoxic, non-hyperplastictoxic, and non-hyperplasticatoxic. The glands showing marked hypertrophy were included with the hyperplastic goiters. Following this classification for the 2917 new cases coming to operation between January 1, 1909, and January 1, 1913, 42.8 per cent. were hyperplastic and 57.2 per cent. were non-hyperplastic. Of the hyperplastics 99.2 per cent. were toxic and 0.8 per cent. were atoxic. Of the non-hyperplastic 23.3 per cent. were toxic and 76.7 per cent. were atoxic.

While the association of the constitutional symptoms with non-hyperplastic goiter was to a certain extent a personal equation, this was to a limited degree true for the cases having hyperplastic thyroids. The estimation that 23.3 per cent. of the non-hyperplastic goiters were toxic was made on a conservative basis.

Patients coming under observation with non-hyperplastic toxic goiter gave a history of having first noted the goiter at the average age of 22 years, and the evidence of intoxication at the average of 36.5 years. The corresponding ages for hyperplastic goiter were respectively 32 and 32.9 years.

That non-hyperplastic goiter was noted 10 years earlier in life than hyperplastic goiter, that 14.5 years elapsed between the appearance of non-hyperplastic goiter and the development of notable toxic symptoms, and that the constitutional symptoms were noted but a few months later than the goiter in the patients affected with hyperplastic thyroid was alone sufficient to show that we were dealing with at least two distinct pathological and clinical groups. That one was not the sequence of the other was self-evident.

Are all hyperplastic goiters coming to operation toxic? Throughout the series the number of cases in which the clinician failed definitely to note and attribute constitutional symptoms to the thyroid and which were later diagnosed by the pathologists hyperplastic thyroid varied from 2 cases in 1909 to 4 cases in 1912; 2 of these 4 cases were in children under 4 years of age and could be excluded in considering the hyperplasia of adults. The third case was a girl, aged 15 years, who gave a history of having noticed the goiter, periods of tremor, tachycardia, and palpitation for nine months. However, these symptoms were not attributed to the thyroid previous to operation. The fourth case was a woman, aged 47 years, who gave a history of having noticed the goiter for twelve years, rapid growth during the few months previous to coming to operation and a long train of symptoms, part of which might be attributed to thyroid intoxication. A few cases that had small areas of hyperplasia in the thyroid were excluded because they were still under discussion by the pathologists. The majority of them had moderate toxic symptoms, indicating that the activity of the thyroid was proportionate to the degree of the hyperplasia.

Is hyperplasia of the thyroid more prevalent in the first two decades of life than we have definite knowledge of, perhaps indicating a thyroid activity in response to some demand that cannot be considered far from normal? If so, is this hyperplasia of the thyroid to be sharply distinguished from the hyperplasia associated with Graves' disease, which develops at the average age of 32? I do not believe these questions can be definitely answered at the present time, though there is much evidence suggesting an affirmative answer, at least to the clinical side of the question.

Is the exophthalmos of thyrotoxicosis always associated with hyperplastic goiter? The pathological reports fail to show the presence of hyperplasia in the cases in which exophthalmos was noted by the clinician 6 times in 1909, 4 times in 1910, twice in 1911, and not in a single instance in 1912. In 1912 there were

911 new cases of goiter that came to operation. In most of the exceptions to the rule previous to 1912, we were able definitely to prove that there was an error in noting the presence of exophthalmos.

Should all toxic hyperplastic goiters be included under the term exophthalmic goiter? Possibly there is a small group of cases which should not be included. However, that there is small chance for error in answering this question in the affirmative if we include only those cases coming to operation is indicated by (1) of the cases having diffuse hyperplasia of the thyroid coming under observation from one to three, three to six, six to nine, nine to twelve, twelve to eighteen, eighteen to twenty-four months and over two years from the onset of toxic symptoms respectively, 50, 59, 67, 75, 80, 80, and 87 per cent. had exophthalmos (questionable cases excluded); (2) if we select from any periods in our series 25 consecutive patients having hyperplastic thyroids and mild toxic symptoms, over 50 per cent. have exophthalmos; and if we select from the total number of patients coming to operation during 1911 and 1912 the 25 cases of non-hyperplastic thyroids having the most intense intoxication, exophthalmos is not noted in a single instance. It is quite possible that exophthalmos may be associated with non-hyperplastic toxic goiter, but if so, it is so rare that it must be in a way considered accidental.

Is the symptom-complex accompanying hyperplastic goiter to be directly attributed to disturbed thyroid function? While it has been so considered in this paper only as a matter of convenience for pointing out the association of the clinical and pathological findings, and while I do not wish to enter into a discussion of this subject at the present time, I wish to call attention to a point in support of this theory that, so far as I know, has not hitherto been made, namely, that an individual, aged 22 years, with an adenoma of the thyroid has a definite chance of developing a train of symptoms during the thirty-sixth year so similar to the symptom-complex associated with hyperplastic thyroid that the best-trained diagnosticians are constantly confusing the two conditions.

Can we associate the symptom-complex of non-hyperplastic toxic goiter with any definite pathological change in the thyroid? For the present this question must be answered in the negative.

Correlating the above statistical data, we may safely come to the conclusion that exophthalmic goiter is a definite clinical complex always associated with hyperplasia of the thyroid, and that it should be sharply distinguished from the constitutional state or states that may develop with non-hyperplastic goiter. Still more interesting and convincing is the correlation of a mass of detail with the data given here. This involves too much for a short paper. However, a general conception of the clinical pictures accompanying non-hyperplastic toxic and exophthalmic

goiter is given as an introduction to the paper by Drs. Blackford and Sanford.[2]

For the purpose of quickly presenting the clinical pictures, let us note the parallelism of thyrotoxicosis and alcoholism and assume that there are three toxic elements in the thyroid secretions, one damaging chiefly the nervous system, one the circulatory system, and the other producing exophthalmos. In exophthalmic goiter all three elements are in excess, but the clinical picture is dominated by a nerve toxin, although in individual cases the circulatory toxin or element producing exophthalmos may seem to be in excess.

The intoxications from non-hyperplastic goiter may be divided into two merging groups: (1) a group in which the cardiac toxin predominates, in which the clinical picture closely resembles and in many instances cannot be differentiated from the cardiovascular complex resulting from alcoholic, luetic, septic, and other well-known toxins; (2) a group more closely approaching the picture of Graves' disease and including the cases that have been erroneously so diagnosed by the mass of the profession.

The average lapse of time between the appearance of non-hyperplastic goiter and toxic symptoms is 14.3 years. That the patient comes under observation three years later indicates that the onset is usually insidious. Nervousness, tremor, loss of strength and weight, as a rule, develop slowly, but may appear suddenly long before definite evidence of myocardial damage. The administration of iodin may cause the sudden appearance of those symptoms with myocardial insufficiency much as they might follow the prolonged drinking bout of an old toper who had not previously shown decided evidence of chronic alcoholism. In some cases the clinical aspect, as noted above, closely approaches that of exophthalmic goiter. However, the symptoms are less complex, less definitely associated, and except for a damaged heart, less intense. There is much evidence to suggest that during the 14.5 years previous to the onset of definite toxic symptoms many of the cases of non-hyperplastic thyroid may be compared to the alcoholic tippler in that if the soil is right they develop arteriosclerosis, in many cases showing the combined picture of thyrotoxicosis and arteriosclerosis.

The development of a typical syndrome of Graves' disease in a case having a definite history of simple goiter means that a hyperplastic goiter has been superimposed upon the simple type.

The onset of exophthalmic goiter is, as a rule, relatively acute and the course of the disease fairly definite. The clinical picture early in the history is that of a toxin acting directly on the more vital organs, more notably the central nervous and vascular systems. Later it is made more complex by the interaction of those organs whose functions have been directly disturbed by the toxin. The order of onset of the most important symptoms based

[2] A Demonstration of a Depressor Substance in the Serum of the Blood in Exophthalmic Goiter, read before the Association of American Physicians, May, 1913.

on the average of our series is as follows: (1) cerebral stimulation, (2) vasomotor disturbances of the skin, (3) tremor, (4) mental irritability, (5) tachycardia, (6) loss of strength, (7) cardiac insufficiency, (8) exophthalmos, (9) diarrhea, (10) vomiting, (11) mental depression, (12) jaundice, and (13) death.

If the average course of the intoxication be represented by a curve the greatest height is reached during the latter half of the first year, and then suddenly drops to the twelfth month. In many instances it reaches the normal base-line during the next six months. More often it fluctuates with periods of exacerbation for the next 2 to 4 years. Secondary symptoms and exophthalmos may remain, but the active course only rarely continues over 4 years without distinct intermissions. Compare the striking resemblance of the character, order of onset, and course of this train of symptoms with that resulting from the heavy use of alcohol by a susceptible individual over a corresponding period of time. Near the crest of the curve any shock, operation, etc., that treats the patient to another drink may result in tremens or death.

In the average course after the first year the symptoms that may be attributed to long-continued intoxication rather than to a high degree of acute intoxication, *i. e.*, those from the more chronic types of heart, liver, and degeneration of the kidney enter strikingly into the clinical picture. In attempting to construct a composite curve we find that the curves for those symptoms that we can readily attribute to a high degree of immediate intoxication from the thyroid gradually drop while the curves for those findings attributable to a long-continued intoxication of a lower degree gradually rise.

In a later paper I will point out that there is much evidence to suggest that the sudden onset of the toxic symptoms is preceded by a period during which the patient is gradually habituated to the disturbed function of a developing hyperplastic thyroid and that following the disappearance of the clinical manifestations of the intoxication, the patient is still taking care of the products of an overactive gland and if this overactivity with or without clinical manifestations, continues sufficiently long in an individual prone to arterial degeneration, arteriosclerosis with secondary contracted kidneys, high arterial tension, etc., will ultimately develop. The picture of thyretoxicosis from both hyperplastic and non-hyperplastic goiters may be compared to that from alcoholism in its various degrees and manifestations varying with the dose, length of administration, and susceptibility of the individual.

While the weight of the evidence seems to indicate that, whatever the primary cause, the symptom-complex of exophthalmic goiter is directly attributable to hyperplasia of the thyroid, I wish to repeat that I have so considered it in this paper only as a matter of interest and convenience in associating the pathological and clinical findings.

A DEMONSTRATION OF A DEPRESSOR SUBSTANCE IN THE SERUM OF THE BLOOD OF PATIENTS AFFECTED WITH EXOPHTHALMIC GOITER.[1]

By J. M. Blackford, M.D.,
and
A. H. Sanford, M.D.,
Mayo Clinic,
Rochester, Minnesota.

During the past year we have conducted a series of experiments with a view to throwing further light on the relation of the secretion of the thyroid to exophthalmic goiter. We have studied chiefly the cardiovascular effects on the dog of intravenous injections of sterile non-hemolytic blood-serum from nervous individuals and from patients affected with exophthalmic goiter. Also, numerous saline extracts of goiter have been injected intravenously into dogs and the effects on the blood pressure studied.

Gley[2], in 1911, announced that the serum of certain cases of exophthalmic goiter produces marked cardiac depressor action. He showed, too, that a first injection of potent exophthalmic serum conferred a tolerance of such a nature that subsequent injections of the same serum during the same experiment produced little or no effect.

We have attempted to follow out Gley's researches, injecting intravenously into dogs the serum procured from patients affected with exophthalmic goiter. The effect on blood-pressure was recorded graphically on a long paper kymograph in the usual manner, using the left carotid artery for the arterial cannula. All injections were made into the right femoral vein. The right vagus was exposed and stimulated by induction shock in certain experiments. Blood was obtained by sterile technic from the median basilic veins of the patients, collected in sterile flasks and the serum allowed to separate in the cold. The manifest difficulty that must always be encountered in such work, *i. e.*, the impracticability of obtaining a large supply of blood from each case, has somewhat hindered certain experiments, but we believe that our results are sufficiently interesting to justify reporting.

Gley states that 5 c.c. of serum per kilo dog weight must be used to obtain the best results. We did not have sufficient serum for such large dosage, but obtained excellent results with smaller doses. We have injected $2\frac{1}{2}$ to 4 c.c. serum per kilo dog weight as an average dose, and except when stated to the contrary, this has been the amount of serum.

[1] Read before the Association of American Physicians, Washington, D. C., May, 1913.
[2] Jour. de Phys. et de Path. Gén., 1911, xiii, 928 to 941; Cleret, ibid., pp. 955 to 970.

We have used for these experiments the sera from twenty-eight patients having exophthalmic goiter. Other sera examined have included those from normal individuals, from patients having goiters without apparent intoxication, and from patients presenting the picture of a long-standing intoxication, presumably due to adenomas of the thyroid. Only the sera from patients with active symptoms of exophthalmic goiter and with markedly hyperplastic glands, as shown by microscopic examination have produced in the dogs injected any definite symptoms of cardiovascular depression.

The curves produced by the sera from patients affected with exophthalmic goiter have naturally fallen into three groups:

Group I. Those sera causing more than 30 mm. of Hg. drop in blood-pressure.

Group II. Those sera causing a drop in blood-pressure, but less than 30 mm. of Hg.

Group III. Those sera causing no appreciable drop in blood-pressure.

The significance of this classification was observed only after an analysis of the individual cases.

Group I. *Six Sera Causing Drops in Blood Pressure of More than 30 mm. of Hg.* The four curves in Chart 1, all of which produced drops in blood-pressure of more than 30 mm. of Hg. when injected in doses of 2.5 c.c. per kilo dog weight, were obtained by injecting sera from patients who were at or near the height of an early and severe intoxication, as shown by the following summaries of the case histories:

CASE 69,123.—Female, aged twenty years. Three months before (March, 1912) noticed suddenly all the typical cardiac, nervous, and muscular symptoms of Graves' disease. Rapid progress during one month to acute vomiting, with great loss of strength. During the third month vomiting ceased, but all other symptoms were marked. (Experiment conducted on dog 253.)

CASE 69,198.—Female, aged fifty years. Slight goiter noted one year before (May, 1911). Definite typical symptoms of exophthalmic goiter began six months before with loss of weight, weakness, and nervousness. Two months before violent crisis, with vomiting, the patient remaining in an acute condition for one week, since then vomiting in spells. In bed most of the time. Loss of thirty pounds in weight in two months. Patient had not noted exophthalmos, which was moderately evident. (Experiment conducted on dog 259.)

CASE 67,993.—Male, aged seventeen years. Three months before (February, 1912) began to lose weight, and all the usual symptoms became evident and rapidly progressed. A month later goiter was noted and the patient forced to bed by weakness. In bed one month, then slight improvement, and has been able to be out of

bed the past month, though a marked intoxication is still present. (Experiment conducted on dog 249.)

CASE 68,628.—Female, aged twenty-three years. Six months before (January, 1912) developed nervous and cardiac symptoms and exophthalmos. She rapidly became worse, and at present shows marked intoxication. Diarrhea for one month. Marked loss of strength and fifteen pounds loss of weight. This patient died in an exacerbation following a single ligation. Unfortunately autopsy on this patient was refused. (Experiment conducted on dog 192.)

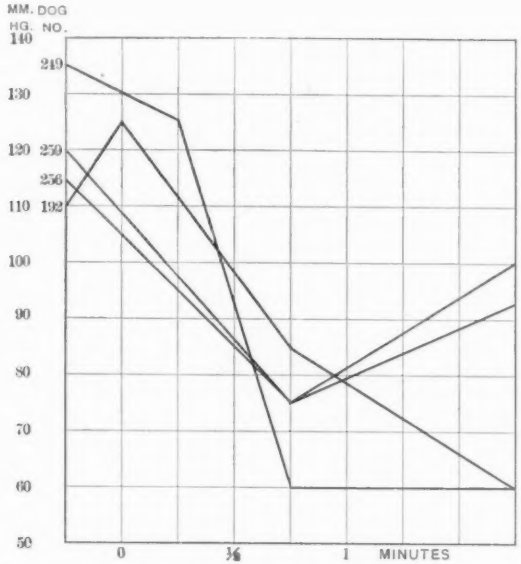


CHART 1.—Drops in blood-pressure of more than 30 mm. after injection of sera from patients in the stage of acute intoxication from exophthalmic goiter.

We believe these histories show conclusively that the four cases were all acute and severe intoxications. Clinical diagnoses in these as well as the following cases have been confirmed by pathological examination of the goiters except the one which terminated fatally.

The two cases shown in Chart 2 are interesting exceptions. One was a fairly acute intoxication of only moderate severity; the other was a chronic intoxication of marked severity. The case histories are as follows:

CASE 75,496. Male, mulatto, aged thirty years. Past history, gonorrhea, syphilis (positive Wassermann), and some alcoholic excess. Two years before (November, 1910) began to lose weight

and strength, and noticed nervous, cardiac, and eye symptoms. Rapid progress to an extreme crisis, with prostration, vomiting, and diarrhea. Then recovery during six months; able to do some work, but still had marked intoxication with a chronic diarrhea.

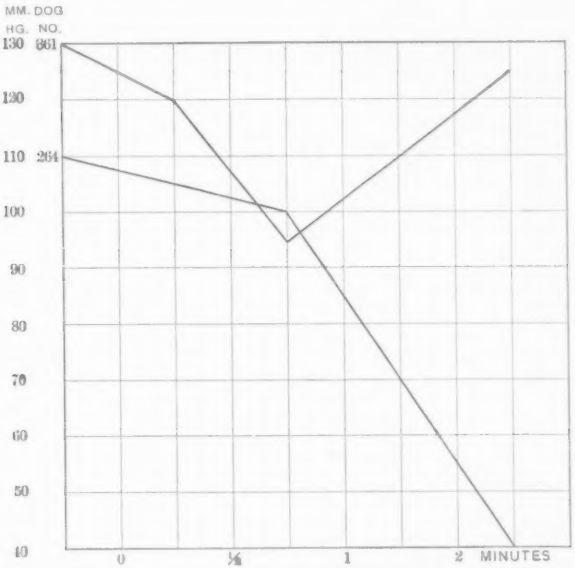


CHART 2.—Drops in blood-pressure of more than 30 mm. after injection of large doses of sera from patients with moderate intoxication from exophthalmic goiter.

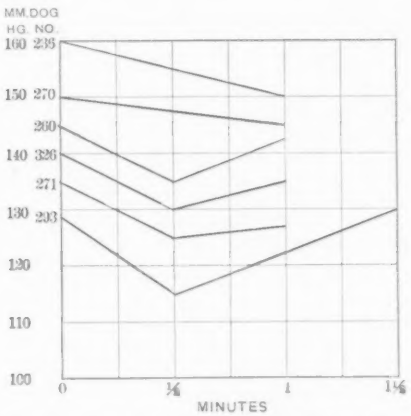


CHART 3.—Drops in blood-pressure of less than 30 mm. after injection of sera from patients not at the height of intoxication from exophthalmic goiter.

Weight forty pounds below normal. (Experiment conducted on dog 361.)

CASE 69,619.—Female, aged nineteen years. Nine months before (October, 1911) had to stop school on account of weakness, dyspnea and nervousness. Symptoms progressively worse until forced to bed six months before. After a rest she improved steadily, and presents a clean-cut but not marked picture of exophthalmic goiter. (Experiment conducted on dog 264.)

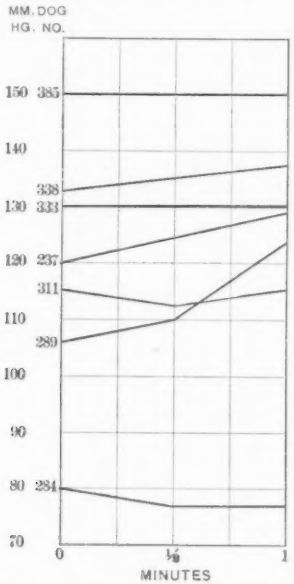


CHART 4.—No effect on blood-pressure following injection of sera from patients with symptoms of intoxication from exophthalmic goiter, but not at or near crisis.

From the two preceding histories we may judge that neither case was extreme. On examining our records we find that the doses of serum given each dog were about three times that used to secure the marked effects shown in Chart 1. Again, we may note that the first case (75,496) was a chronic and severe one, but gave only a 35 mm. drop in blood-pressure, thus almost admitting it into the next group. The second case (69,619) gave a marked fall in blood-pressure, and though not very severe, was not far past a crisis when the blood was taken.

Group II. *Ten Sera Causing Drops in Blood Pressure of Less than* 30 *mm. of Hg.* Chart 3 shows the curves resulting from injections of six of these sera which caused a fall in blood-pressure of less than 30 mm. of Hg., but which apparently contained a slight amount of the depressor agent. Eight of these ten patients had

been afflicted with the disease for more than a year and none of them seemed near any marked exacerbation. In general it may be stated that these cases were of longer standing and with more pronounced intoxication than those in the following group. Two typical histories from this group are as follows:

CASE 68,883.—Male, aged thirty years. Appendectomy had been done eighteen months before (January, 1910), following which symptoms of exophthalmic goiter promptly appeared and progressed during six months to an extreme intoxication with vomiting, diarrhea, and prostration. Loss of forty pounds in six months. For the past six months steady improvement, and now is nearly normal in weight, though still affected with definite Graves' disease. (Experiment conducted on dog 253.)

CASE 67,283.—Female, aged thirty-six years. Tremor noted for several years. Always more or less nervous. Increased irritability and gradual loss of strength was noted six months before (November, 1911). No dyspnea. Slight diarrhea during the past month. Working steadily to date. (Experiment conducted on dog 236.)

Thirteen Sera Causing no Appreciable Drop in Blood-pressure. Chart 4 shows six curves as typical of the thirteen inert sera which fall into this group. None of the patients seemed to be near a crisis, and eight of them had been sick less than nine months.

These experiments seem to indicate that patients affected with exophthalmic goiter who are suffering from a marked degree of intoxication at or near the height of the clinical curve of the disease (Plummer) possess serum which has a powerful depressor action. The authors have failed to demonstrate this depressor action by similar means in normal sera, or in sera from patients not having markedly hyperplastic thyroids. Also sera from patients with exophthalmic goiter not at or near the crest of the wave of intoxication are less potent or may be entirely inactive.

Since it was not always thought best to bleed very sick patients, only a small number of experiments have been made with sera from patients with severe intoxications. Yet it may be of interest to know that most of the patients that were bled experienced considerable relief from their subjective symptoms after the bleeding.

The results of intravenous injections into dogs of saline extract of ninety goiters of various kinds from human patients have also been made. These experiments may have some bearing on the action of the depressor sera and a brief report of the results is herewith appended.

Intravenous Injections of Saline Extracts. Experiments with extracts of forty-eight exophthalmic thyroids have shown that the markedly hyperplastic goiters considered typical of Graves' disease have a more powerful depressor action than that of the extract of any normal organ examined, including muscle, liver, spleen, pancreas, breast, testicle, thyroid, etc. The fall in blood-pressure

averages 60 mm. of Hg., and is often considerably more, whereas that from other tissues in any comparable dosage is usually less than 25 mm.

Extracts of adenomas of the thyroid, of simple colloid goiters, and of normal thyroids likewise have a depressor action, which, however, has not been found so marked as that produced by extracts of exophthalmic thyroids. Injections equivalent to as much as 5 gm. per kilo dog weight do not cause a fall as great as that of the extracts of exophthalmic goiters in doses of 0.5 gm. per kilo dog weight.

The first injection of any extract of fresh goiter, as of most extracts of tissue, confers a marked degree of tolerance to subsequent injections of the same material during the same experiment.

As is well known, peptone solutions cause a marked fall in blood-pressure on intravenous injection, and subsequent injections show that a tolerance has been established similar to that produced by extracts from goiters. The depressor action of peptone solution is not, however, affected by a previous dose of the extract of exophthalmic goiter, nor is the action of the extract of exophthalmic goiter affected by a previous dose of peptone solution. On the other hand, it is interesting to note that the depressor action of the extract of an exophthalmic goiter is much diminished by a previous dose of potent serum from a case of toxic exophthalmic goiter, and the reverse, judging from a limited number of experiments, is equally true. In other words, a crossed tolerance seems to exist between the depressor action of extract of exophthalmic goiter and of exophthalmic serum. It seems probable, therefore, that the depressor agent in the extract of exophthalmic thyroid and that in the serum from a case of exophthalmic goiter are of the same nature.

No attempt has yet been made to identify the chemical nature of the depressor substances in these extracts of thyroids or of those in sera of patients affected with exophthalmic goiter. From certain experimental evidence it seems that the substance is neither cholin nor ordinary peptone.

Conclusions. We believe that the work submitted justifies the following conclusions:

Fresh extracts made from exophthalmic thyroids contain a powerful depressor substance.

A powerful depressor substance likewise exists in the sera obtained from certain cases of exophthalmic goiter.

The latter substance is present in direct proportion to the clinical acuteness and severity of the disease.

The sera from patients with non-hyperplastic thyroids do not have a depressor action.

After an active depressor dose of the serum from a case of exophthalmic goiter the depressor action of the extract of an exophthalmic goiter is weakened or abolished. The converse is also true.

ANTITYPHOID VACCINATION.[1]

By Frederick F. Russell, M.D.,

MAJOR IN MEDICAL CORPS, UNITED STATES ARMY, AND PROFESSOR OF BACTERIOLOGY IN ARMY MEDICAL SCHOOL, WASHINGTON, D. C.

The subject of antityphoid vaccination has a great and promising field of usefulness in the United States, both in civil life and in the Army. We shall consider in turn the history of the subject, the methods of preparing the vaccine, its standardization and dosage, the indications for its use, the results already obtained, and its probable value in the future.

The basis upon which the practice of antityphoid vaccination has been built is, of course, the observation that one attack of typhoid fever almost invariably gives permanent immunity against subsequent attacks. Of 2000 cases in the Hamburg General Hospital, only 14 persons were affected twice, and but 1 three times (Dreschfeld). In 500 of Osler's cases in which special inquiry was made as to previous attack, it was found to have occurred in 11, or 2.2 per cent. It is interesting to note that although the immunity usually lasts during life, the immune bodies, nevertheless, disappear from the blood of convalescents within a few months.

The harmlessness of inoculating killed typhoid bacilli into human beings was demonstrated in the year 1896 by Sir A. E. Wright in England and Pfeiffer and Kolle in Germany. The publication of Pfeiffer and Kolle's investigations[2] antedates Wright's paper by some months. The researches of Pfeiffer and Kolle were conducted on two men, and were remarkably complete and comprehensive, showing, as far as the laboratory methods of that day permitted, the identity of the immunity following an attack of typhoid fever with that produced by the inoculation of killed typhoid bacilli. Thus early was the precedure placed on a solid scientific basis.

Wright's first paper,[3] curiously, is entitled "On the Association of Serious Hemorrhages with Conditions of Defective Blood Coagulability," and the inoculation of killed typhoid bacilli was apparently a mere incident in a research upon another subject. The following year, however, he reported on the blood changes in 17 persons, following typhoid inoculation.[4] It is in this paper that Wright mentions Haffkine's suggestion to him, made a year previously, that the method of vaccination with bacterial cultures, which had

[1] Read before the Harvey Society, New York, February 8, 1913, and published by permission of the Surgeon-General.

[2] Deutsch. med. Woch., 1896, xxii, 735.

[3] Lancet, London, September 18, 1896, p. 807.

[4] Sir A. E. Wright, British Med. Jour., January 30, 1897, p. 16.

been so successfully used in the prophylaxis of cholera, might, *mutatis mutandis*, be applied to the prevention of typhoid fever. Wright appears to have been convinced by his series of 17 cases that the prevention of typhoid fever by vaccination was a possibility. He suggested at this time (1897), its use in armies and among the personnel of hospitals. This really constitutes the beginning of the present vaccination campaign against typhoid fever. Wright continued his work with enthusiasm, and in 1898, while serving on the Plague Commission in India, vaccinated about 4000 men of the British Indian Army, with excellent results.[5] Soon after his return to England, in 1897, there occurred an extensive outbreak of typhoid fever at the Barming Asylum, Maidstone; and as he himself was unable to go he sent, first, Sir David Semple and afterward Sir William B. Leishman to conduct inoculations on about one hundred of the attendants. There also the results were highly gratifying, since no cases occurred among the inoculated.

Soon afterward, in 1900, came the Boer War, and antityphoid inoculation, having already given such a good account of itself, upon Wright's recommendation its use was authorized by the War Office among the troops destined for South Africa.

The vaccination was voluntary, and, as a matter of fact, is still voluntary in every country except in the United States. Some men were inoculated before leaving England, others on the transport during the long voyage to South Africa, and in a few instances in the field after arrival. For this purpose Wright and Leishman furnished some 400,000 doses, but it is believed that only 100,000 men received one or more.

No complete statistics of antityphoid vaccination in South Africa have ever been published, and they probably do not exist. We know in general that there were 57,684 cases of typhoid and 8022 deaths among 380,605 men.[6] This gives a morbidity rate of 151.56 per 1000, a result which does not differ markedly from our own rates in the Spanish-American War, where no vaccination was in force. In our service a larger number of cases were diagnosticated, but the death-rate was, nevertheless, much less than in South Africa.

TABLE I.

	Total strength.	Cases.	Ratio per 1000.	Deaths.	Ratio per 1000.
English Army, Boer War, 1900 to 1903	380,605	57,684	151.56	8022	21.08
American Army, Spanish War . . .	107,973	20,738	192.6	1580	14.62
Wright's statistics, Boer War . . .	19,069	226	11.84	39	2.04

Wright collected statistics covering the inoculation of 19,069 soldiers.[7] Among this number there were 226 cases of typhoid

[5] Wright, Lancet, London, September 6, 1902, p. 654.

[6] Leishman, Antityphoid Vaccination, Glasgow Med. Jour., 1912, lxxvii, 408.

[7] McCrae, in Osler's Modern Medicine, 1909, ii, and Wright, Lancet, London, September 6, 1902, p. 654.

fever and 29 deaths, while among 150,231 unvaccinated soldiers, there were 3739 cases of typhoid fever, as appears in the following table:

TABLE II.—Boer War, English Troops, Wright's Statistics.

	Number	Cases.	Ratio per 1000.	Deaths.	Ratio per 1000.
Vaccinated	19,069	226	11.84	39	2.04
Unvaccinated	150,231	3739	24.88	?	?

At Ladysmith,[8] the following results were obtained:

		Morbidity.	Mortality.
Vaccinated	1,705	35 cases (2.05 per cent.)	8 deaths (0.47 per cent.)
Unvaccinated	10,529	1, 489 cases (14.14 per cent.)	329 deaths (3.13 per cent.)

At Modder River[9] there occurred 26 cases among 2335 vaccinated (11.1 per cent.) and 257 cases among 10,981 unvaccinated (23.4 per cent.).

Wright considers that the incidence of the disease was diminished about one-half and the mortality even more. His conclusions, however, were based upon incomplete statistics, and were not accepted at the time by his colleagues in the service. The frightful death-roll remained in spite of explanations. It appeared to have been impossible during the war to keep accurate records or even to vaccinate systematically, and consequently the whole question was left in considerable confusion. This was made worse by the receipt of many unfavorable reports: some asserting that the vaccine did no good, others maintaining that it actually increased the number of cases and deaths.[10] Before the end of the war, as a result of this unfavorable attitude, the British War Office suspended the practice of inoculation and appointed a commission to reinvestigate the whole question. Fortunately this commission, under the chairmanship of Dr. C. J. Martin, of the Lister Institute, included in its membership Sir William B. Leishman, to whom fell the experimental part of the proposed investigation. He conducted extensive experiments at Aldershot in regard to dosage and the changes in the blood serum following inoculation. More recently additional studies have come from his laboratories at the Royal Army Medical College, and the importance of this work of Leishman's can scarcely be overestimated, and although he made only a few changes in Wright's vaccine, they were important ones.

The commission in their statistical studies and experimental work at Aldershot obtained evidences of a considerable degree of protection, and their interim report, rendered in 1904, was decidedly favorable. It introduced accurate and practical methods of obtain-

[8] Report of Committee on Antityphoid Vaccination, Bull. de l'Acad. de Méd. de Paris, January 24, 1911.

[9] Ibid.

[10] A. Crombie, Lancet, London, 1902, i, 1201, and 1902, ii, 436.

ing reports from twenty-four regiments, totaling almost 20,000 men, and, as the results have shown, the work was successful in rehabilitating an almost discredited procedure. As a result, inoculations were resumed in certain selected regiments, to which a medical officer, especially trained in typhoid diagnosis, was permanently attached. By this means, in a comparatively short time, accurate records were obtained. As many volunteers as possible were vaccinated before the regiments left England for India, and efforts to obtain additional volunteers were continued at the Indian stations until the greater number of the men were vaccinated, many regiments having as many as 90 to 100 per cent. protected.

American Experience. For some years we had followed the work of Wright and Leishman with interest, and Wright's visit to this country in 1907 added to our knowledge of his work with vaccines, although at that time Wright was more interested in vaccine therapy in general than in typhoid prophylaxis. We, however, as military sanitarians, always with the possibility of a war confronting us, were more taken with Wright's former advocacy of antityphoid vaccination than with his newer, brilliant theories and discoveries.

The necessity for some means of preventing, or at least controlling, typhoid fever in military camps, in addition to sanitary measures, was a continual spur, driving us on to investigate everything which offered any hope of success. It was, therefore, with great interest that we followed the results obtained by Colonel Leishman[11] among troops of the Indian Army.

In 1909 Leishman published the first comprehensive report of the results of vaccination in certain selected Indian regiments (see accompanying table).

The experience of the 17th Lancers, which had been brought to our attention by Colonel Leishman early in 1908, was so striking that we felt much encouraged about the possibility of having at last an effective propyhlactic, and so began to take an active interest in the vaccine. The writer had been stationed at the Army Medical School only a few months when the late Surgeon-General Robert M. O'Reilly directed him to make preparations to try out the method on our own troops.

As the quickest and best way of beginning, orders were issued in June, 1908, for him to proceed to London, where he could learn from Colonel Leishman and his assistants, at the Royal Army Medical College, their method of preparing the improved vaccine. There he was given the run of the laboratory and was given every facility for learning their methods, including a transfer of the culture (Rawlings) used in preparing the vaccine.

[11] Journal Royal Army Medical Corps, London, 1907, viii, 463, and 1909, xii, 166.

TABLE III.—Showing the Results of Antityphoid Inoculation in Sixteen Units of the British Army, up to June 1, 1908.

Unit.	Medical Officer.	Station.	Total strength (actual).	Inoculated.			Non-inoculated.		
				Number.	Cases.	Deaths.	Number.	Cases.	Deaths.
2d Royal Fusiliers	Capt. A. B. Smallman	Trimulgherry	1,013	196	10	1	815	59	9
17th Lancers	Capt. E. J. Luxmore	Meerut	616	322	3	0	294	71	12
Brigade, R. A.	Capt. E. G. Lithgow	Pindi (from Transvaal)	370	60	0	0	310	7	0
14th Hussars	Lieut. C. E. Fawcett	Bagnalore	647	386	2	0	261	4	1
2d Dorsets	Lieut. E. G. Anthoniss	Wellington	1,107	199	1	0	908	6	0
3d Coldstream Guards	Lieut. J. H. Graham	Cairo	705	569	1	0	136	13	1
2d Leicesters	Lieut. H. S. Sherren	Belgaum	963	346	3	1	617	17	1
1st Connaught Rangers	Lieut. A. D. O'Carrol	Dagshai(from Malta)	483	300	0	0	183	2	1
3d Worcesters	Lieut. W. H. Forsyth	Wynberg	900	220	0	0	680	3	0
1st Dragoon Guards	Lieut. G. H. Stevenson	Umballa	592	450	0	0	142	0	0
1st Yorks	Lieut. de C. O'Grady	Cairo	893	470	0	0	423	0	0
1st Suffolks	Lieut. J. B. G. Mulligan	Malta	900	400	0	0	500	0	0
3d Royal Rifles	Lieut. R. W. D. Leslie	Crete	879	190	0	0	689	0	0
2d Bedfords	Lieut. C. M. Drew	Gibraltar	700	320	0	0	380	3	1
Brigade, R. A.	Lieut. A. S. Littlejohns	Pretoria	375	247	1	0	128	2	0
1st Lan. Fusiliers	Lieut. F. D. G. Howell	Chakrata	940	796	0	0	144	0	0
		Totals	12,083	5473	21	2	6610	187	26

CASE-INCIDENCE PER 1000.

	Inoculated.	Non-inoculated.
Among the whole of the above sixteen units	3.8	28.3
Among the "exposed" units, that is, in which cases of enteric had occurred	6.6	39.5
"Exposed" units, less Royal Fusiliers (the unit inoculated with the "old vaccine")	3.7	32.8

SUMMARY. There are only 4 cases among the above 21 which had received two doses of the new vaccine; all recovered; 3 of the 4 had been noted as extremely mild, and the diagnosis of enteric in one of these was doubtful.

Later (1908) a trip was made to Berlin, where at the Institute for Infectious Diseases he learned of the German experience with typhoid prophylactics. The complete report of the German investigations, published in 1905, is accessible, and will be passed over quickly.[12]

The occasion for the German investigation was the excessive prevalence of typhoid fever among the colonial troops in southwest Africa. All attempts to control the epidemic by the usual sanitary methods having been unsuccessful, recourse was had to vaccination. The Institute for Infectious Diseases was intrusted with the task of investigating the vaccines already proposed, the selection of some reliable method, and the preparation of the vaccine, should one be decided upon.

Comparative tests were made of vaccines prepared according to the methods of Pfeiffer and Kolle, Wright, Neisser-Shiga, Wassermann, and Bassenge-Rimpau by the staff of the Institute,

[12] Veroffent. a. d. Gebeit. des Militar-Sanitatswesens, Berlin, 1905, Heft 28.

consisting at that time of Professors Kock, Kirchner, Gaffky, Doenitz, Kolle, and Wassermann.

Small groups of men were immunized with each vaccine and the blood-serum subsequently tested for bacteriolytic amboceptors by Pfeiffer's test and for agglutinins by the usual techinque. Although the bacteriolysins and agglutinins did not run parallel, they found that the Pfeiffer-Kolle vaccine gave a much greater degree of protection than any other, and it was therefore adopted. They objected to Wright's vaccine because of his use of broth cultures, since it is well known that bacterial contaminations are difficult to avoid or to detect in fluid media.

The Pfeiffer and Kolle vaccine consisted of a salt-solution suspension of fresh agar cultures of typhoid of such a strength that 1 c.c. contained two normal loopfuls, or 4 mg. of fresh bacterial substance. The bacteria were killed by heating the flasks, from one and a half to two hours, in an incubator regulated for 60° C. After tests for sterility, 10 per cent. of a $\frac{1}{20}$ solution of phenol was added. The dose used at first was one, two, and three loopfuls of killed culture contained in 0.5, 1.0, and 1.5 c.c. of vaccine; as this dosage, however, produced severe general and local reactions, it was subsequently reduced to 0.4, 0.8, and 1 c.c. The interval between doses was ten days; the site of inoculation was the breast at the level of the second rib.

This vaccine was used in the German Colonial Army, which consisted at that time of about 16,500 men, of whom 7287, or less than one-half, volunteered for the inoculation. Among this number there were 1277 cases of typhoid,[13] and a study of their distribution shows clearly the undeniable advantages of prophylactic inoculation, even though the results were not nearly so good as have since been obtained in India and in our own country. The weak point of the German vaccine lay, apparently, in the high temperature at which it was killed and in the excessive dosage.

One may briefly and roughly summarize their results by saying that there was a reduction among the vaccinated of one-half in the number of cases, a much higher percentage of light attacks, 50 to 36, and a much lower percentage of fatal cases, 6.4 to 12.8. If we distinguish between those receiving one, two, and three doses we find that the percentage of fatal cases was 60, 33, and 8 respectively. This is in agreement with later experience in showing that little protection is to be expected from one dose. Among the uninoculated there was 1 death in every 7.8 cases, while among those receiving three doses there was not only a lower morbidity but only 1 death in every 36 cases.

Kuhn[14] concluded that the immunity was largely lost after one

[13] Shoemaker, Herero Campaign, International Clinics, Philadelphia, 1909, 19th s., ii.
[14] Ibid.

year, since after that time there was little difference between the sick- and death-rates of the vaccinated and unvaccinated.

Colonel Firth, R. A. M. C.,[15] reasoning from similar data, found that the vaccines in use today in India maintain a high degree of protection for at least two and a half years.

The history of antityphoid vaccination can be divided into two stages. The first period includes the early experimental work of Pfeiffer, Kolle, Wright, and Wright's immunization of 4000 men of the British Indian Army, the Boer War and the German campaign against the Hereros. The most accomplished during this period was the reduction of the morbidity to about one-half among the vaccinated and a rather greater diminution of the case mortality.

Explanation of Early Failures. Disappointment at the poor showing made by antityphoid vaccination during this first period was widespread, and for a time prevented any serious consideration of its further use. The loss of interest was due to two things: (1) The undoubted failure to secure anything like absolute protection against infection and death, and (2) what was perhaps even more important, Wright's unfortunate doctrine of a negative phase. To consider, first, the failure to secure a high degree of protection, we now know from the writings of Colonel Leishman,[16] that much of the vaccine sent to South Africa, was, from our present point of view, overheated in its preparation or otherwise rendered inert. Later investigations by Colonel Leishman, Majors Harrison, Grattan, and others have shown that overheated vaccines are almost worthless. Poor and incomplete immunity, due to faulty vaccines, is therefore a preventable condition, and this source of error once known, its avoidance and the regular production of efficient, powerful vaccines is a simple matter.

Wright's Doctrine of the Negative Phase. The other cause of disappointment and lack of interest was the doctrine of the negative phase. The doctrine that vaccination could actually and materially increase one's susceptibility to infection for a time was generally believed, and was advocated by none more emphatically than by Wright himself. It mattered not that experience with other vaccines had shown no increase of susceptibility beyond the normal. Wright built up the theory of a dangerous negative phase upon questionable determinations of the opsonic index and upon certain phenomena observed in the production of diphtheria and tetanus antitoxin in animals. It is well known that the antitoxin content of the blood of the animals used will fall from a previously high level after each administration of toxin. The conditions, however, are not at all comparable: in human beings

[15] Journal Royal Army Medical Corps, 1911, xvi, 589.

[16] Harben Lecture, Antityphoid Vaccination, Journal Royal Institute Public Health, London, July, August, and September, 1910.

no such enormous doses are used, and further, in the beginning of the immunization of a horse, when the doses are small and widely spaced, it is doubtful if there be any reduction of resistance below the normal level. Upon such theoretical grounds, and upon isolated instance of severe typhoid fever following immediately after vaccination, was this doctrine built up, and, very curiously, it was uncritically accepted by the greater part of the medical world. Wright even went so far as to discover a condition of increased susceptibility to smallpox immediately following vaccinia. However, vaccination against smallpox in the presence of an epidemic was too firmly rooted to be successfully questioned. The doctrine of the negative phase in practical immunization appeared only in relation to typhoid fever; nothing was heard of it at that time in connection with bubonic plague and cholera, except from Wright.

In an article published by him in 1902,[17] on the results of vaccination in South Africa, the following is found: "In bringing this summary to a conclusion, I am anxious to reëmphasize a point already emphasized by me in previous papers: that there is, in connection with all protective inoculations, a risk to be considered. There is the risk that (1) in the case where the patient's resistance is naturally low, or has been reduced, as is often the case, by a previous attack of typhoid fever; (2) in the case where the patient is inoculated with a full dose of vaccine in actually infected surroundings; (3) in the case where the patient is inoculated with an excessive dose, or is reinoculated too soon, the system may be left more open to infection at a period when it stands in need of protection. The facts seem to me to indicate the reality of this risk."

In a hasty search through the later publications of Wright few definite statements can be found to justify his former attitude. In later papers he speaks quite guardedly, observing that the risk of a negative phase comes seriously into consideration only when excessive doses of vaccine are employed, or when the prophylactic inoculations are undertaken in the actual presence of infection."[18]

He adds that the remedy lies near at hand, and consists of a reduction in the size of the dose.

In the preface to his book on *Studies on Immunization*, published in 1909, he no longer insists on the dangers of increased susceptibility, but speaks of the practibility of controlling the negative phase and of immunizing a patient without risk or appreciable delay. He even goes farther and approves the therapeutic use of antityphoid vaccine, a position which would have been absurd if vaccination lowered the patient's resistance to typhoid toxins.

[17] Lancet, London, September 6, 1902, p. 654.

[18] Wright's Studies on Immunization, London, 1909, and Boston Med. and Surg. Jour., May 9, 1903.

The best discussion of the subject from the opposite point of view we owe to R. Pfeiffer,[19] who questioned Wright's data, based as it was principally upon the opsonic index. Pfeiffer and Friedberger convinced themselves that guinea-pigs inoculated with large doses of vaccine did not show any increased susceptibility to intraperitoneal infection with living cultures, but, on the contrary, their resistance was distinctly increased, and that this change was apparent within a few hours. This increase of resistance continued to be present up to the time when the formation of specific antibodies began. These results are in agreement with the earlier work of Pfeiffer and Isaeff[20] on non-specific resistance as contrasted with specific immunity.

What can be said on the practical side of the question? Is it true in actual practice that vaccination increases susceptibility to infection? A definite and conclusive negative answer can be made to these questions. Leishman[21] relates his experience in inoculating one hundred attendants at the Barming Asylum, Maidstone. There, if ever, evidences of increased susceptibility would have been present. The inoculations were made, at the height of the epidemic, with doses of vaccine considerably larger than are now used. Yet no single case occurred, and Leishman was convinced that the dangers of a negative phase were more theoretical than real.

Cullinan[22] in 1901 vaccinated 500 persons at the Richmond Asylum, Dublin, during an epidemic lasting five months; among these only 1.36 per cent. contracted the disease, and almost all were in the incubation stage when inoculated; on the other hand, of the 114 uninoculated nurses, 14.9 per cent. became infected.

More recently, Spooner[23] in Boston, and Hachtel and Stoner in[24] Baltimore have immunized the personnel of the Boston and Baltimore hospitals. This is, of course, equivalent to vaccinating in the presence of an epidemic, yet they deteced no indication of increased susceptibility immediately following vaccination.

Spooner[25] has recently used vaccine, during an epidemic, with satisfactory results. He writes as follows: "The water-supply of a limited number of people in a small Vermont village became contaminated with the typhoid organism from the excreta of an isolated individual who had died from the disease six months prior to the epidemic. The original primary cases, 17 in number, appeared simultaneously. Within a week 29 of the remaining 48 who had been exposed to the disease through the water-supply had been

[19] Centralbl. f. Bakteriol., 1908, 1 Abt., Referate, xl, 712.
[20] Zeitschr. f. Hyg. u. Infectionskrankh. Leipzig, 1894, xvii, 355.
[21] Harben Lecture, September, 1910.
[22] H. M. Cullinan, Antityphoid Vaccination during an Epidemic in Dublin, reported by Wright, British Med. Jour., October 26, 1901, p. 1226.
[23] Jour. Amer. Med. Assoc., 1912, lix, 1359.
[24] Ibid., 1364.
[25] Trans. Assoc. Amer. Phys., 1912, xxvii, 343.

inoculated; 19 remained uninoculated. Among the latter, 5 cases developed; among the former, 1. This case presented his first symptoms immediately following the first dose of vaccine, and the disease ran a mild course."

The immunization of those in the immediate neighborhood of typhoid fever patients brings up this question in acute form. We have, so far as possible, immunized all contacts and have seen only good results. Many, however, still hesitate to practice in typhoid fever what is regularly done in the case of variola.

Peterson[26] relates the following: "An interesting fact, which in my mind removes any doubt of its efficacy, was that in one house there were fourteen occupants, seven of whom were in the acute stage of typhoid. The remaining were immunized with no further development of typhoid in the house. The house and surroundings were about as unsanitary as any I ever saw or expect to see."

As we look back upon this dark period we can see that the unfortunate doctrine of a harmful negative phase arose in part, at least, from a false interpretation of the relative failure of vaccination in South Africa. That failure we now believe was due not to any false or dangerous element in the principals of prophylactic vaccination, but to the use in improper dosage of an overheated and comparatively inert vaccine, which simply failed to give the the desired protection.

Leishman and his co-workers discovered the fault and found the remedy. They reduced the amount of heat used in killing the cultures and also diminished the dose. At Aldershot they tried out various doses upon human beings and adopted that now used in practically all countries, 500,000,000 and 1,000,000,000 bacilli, as this quantity was sufficient to produce an abundance of immune bodies and rarely caused severe reactions.

The doctrine of a negative phase was so simple, so reasonable, and, if true, so important for everyone to know that it came early to the knowledge of all reading physicians. Backed as it was by abundant statistics from South Africa it was accepted as true by almost everyone, and its overthrow has not yet been fully accomplished. In England and in India little of it is now heard; in this country, in the army and in the naval service, its conquest dates back only three years. In civil life we still hear it referred to by men who have not yet used antityphoid vaccine. Owing to this doctrine, there is in France, both in the Academy of Medicine and in the army, an active and energetic opposition to the use of vaccination in the military and naval services.

The writer's personal experience with antityphoid prophylaxis began, as previously stated, in 1908, when he was ordered abroad by the War Department to study the subject at first hand. In

[26] J. J. Peterson, Control of Typhoid Fever by Vaccination, Southern Med. Jour., 1912, v. 257.

Colonel Leishman's laboratory, in London, he found that vaccine was prepared by growing in broth a single selected strain (Rawlings) of the typhoid bacillus. The flasks used were long, flat bottles which were incubated lying on their sides, giving a thin layer of medium in contact with the air. The bottles of broth, after preliminary incubation to determine their sterility, were inoculated with a pipette from a broth culture. After twenty-four to forty-eight hours' incubation the growth was usually sufficiently heavy to require the addition of a small quantity of plain broth to reduce the bacterial count to the quantity desired, 1,000,000,000 to the cubic centimeter. The counting was done by an ingenious wet method devised by Harrison, using washed red blood-cells from a definite quantity of blood with which to compare the number of bacteria in an equal quantity of emulsion. The vaccine was killed by heating for one hour at 53° C., and after cooling 0.4 per cent. of lysol was added as a matter of safety.

The English vaccine is, therefore, a killed broth culture made from a single strain of the bacillus, which was originally selected because it emulsified well from agar slants. Preliminary trials of this organism showed that it agglutinated well in immune serum, and produced in good quantities all measurable kinds of antibodies in animals and man. This strain is still in use in England and in our military service, and although we have searched from time to time for a strain with greater antigenic properties, none has yet been found.

In Germany the only prophylactic used at all extensively was made according to the method of Pfeiffer and Kolle. Aside from their use of agar media the characteristic of the vaccine is its standardization by the loop method, a normal loop being one which holds 2 mg. of fresh bacterial substance. Experience has shown that a single slant would furnish about ten normal loopfuls and that the quantity of vaccine obtained per test-tube was 5 c.c. This enables one to compare the dosage with that used by the English and ourselves, since we obtain from 15 to 20 c.c. of prophylactic per tube. The German dosage was, therefore, about three or four times as great. Their method of killing and the temperature used are also important for a complete understanding of their vaccine. They also used a single strain of the bacillus, the culture known as 151 being selected from a large number because of its exceptional binding properties. Wassermann particularly has insisted that the property of binding and of producing antibodies is of more importance in the selection of an organism for the production of vaccine than its virulence.

Our own vaccine is made from a single strain of bacillus (Rawlings), and the culture is grown on agar in flasks for eighteen hours. At first, when small quantities only were needed, test-tubes were used, but as the quantities increased Kolle flasks were substituted, each with an agar surface equivalent to twelve tubes.

The culture used is plated out—a dozen colonies are fished on to double sugar-tubes,[27] and from these macroscopic agglutinations are made. Any culture which fails to develop the characteristic appearance on double sugar, or to give a good agglutination, is discarded; from the remaining cultures agar slants are inoculated and the next day emulsified in a small quantity of broth; with this thick emulsion the Kolle flasks are inoculated by means of a large swab. If they show no contamination after eighteen hours' incubation the growth is washed off in a small quantity of salt solution, and, while a sample is being counted, the thick suspension is heated in large flasks in a water-bath for one hour at 53° to 54° C.

The killed vaccine is diluted with large quantities of salt solution until the desired concentration, 1,000,000,000 to the cubic centimeter, is obtained. Finally 0.25 per cent. of trikresol is added as a matter of safety. After aërobic, anaërobic, and animal tests have been made the vaccine is put up for shipment in hermetically sealed ampuls of normal glass.

The aërobic and anaërobic tests for sterility are made with large quantities of vaccine, several cubic centimeters to each tube and plate; the animal tests consist in the inoculation of a mouse and guinea-pig, with 0.5 and 1.5 c.c. for the exclusion of tetanus spores, and a rabbit with three doses at ten-day intervals to determine the immunizing power of the vaccine. The average titer of the agglutinating rabbit serum obtained with the last eighteen batches of vaccine after thirty days was 1 to 18,000.

Morphological tests of purity, using Gram's stain, are made at each stage of preparation, and a few lots of vaccine have been discarded because of contamination with the Bacillus subtilis group, but none have ever been rejected because of the animal tests. They are continued, however, because of the occurrence of a number of deaths from tetanus in India after the administration of plague vaccine. In one case a batch was discarded because it failed to produce bood agglutinations in the rabbit test.

We have used agar cultures because of the ease of detecting contamination and to avoid the injection of extraneous materials contained in fluid media.

The vaccine is killed by heat rather than chemicals, using the least amount possible to obtain sterility, and it is protected against subsequent contamination by trikresol.

Our vaccine is essentially the whole body of the Bacillus typhosus, changed as little as possible in killing, suspended in a convenient quantity of salt solution. Such a vaccine has the merit of simplicity, is readily and easily prepared, and is constant in quality.

What then have been the results obtained with it in protecting human beings?

[27] F. F. Russell, Jour. Med. Research, Boston, 1911, xxv, 217.

We began to use the prophylactic early in 1909, after first submitting the project to a board of officers selected from among the distinguished members of the medical reserve corps of the army, since it was realized from the start that little could be accomplished without the support of the medical profession of the country. This board recommended the introduction of voluntary vaccination, and work began in earnest early in 1909.

All who had seriously studied the subject of bacterial vaccines and typhoid immunity, realized that the use of prophylactic inoculation was theorectically possible and justifiable, but few considered it practical. For the army, however, the question was too important to be slighted, and a repetition of the experiences of the Spanish-American War must be prevented in one way or another.

Antityphoid vaccination was taken up with a firm conviction as to its value, but with many misgivings as to our power to convince others, or to secure sufficient volunteers to give it a fair trial. It is difficult to overcome the inertia of great bodies like the army, and there is always the danger of ignorant and malicious criticism.

The first doses given to the laboratory staff seemed to have a greater importance, and the operation was more momentous than the occasional therapeutic use of other vaccines, since so much depended upon an auspicious beginning.

When the immunization of the laboratory force had been completed, available volunteers seemed for a time to have been exhausted; but the news spread, and practically all of the medical officers in and about Washington volunteered, and, in turn, sent their wives and children, friends and servants. This helped us over the first obstacle, and we began to obtain volunteers from the hospital corps. By the end of 1909, 1887 persons had received the prophylactic treatment, and during the next year (1910) 16,073 additional volunteered. During the first part of 1911 volunteers continued to present themselves in increasing numbers, so that immunized men came to be present in practically every garrison in the United States proper. The measure was no longer strange to the medical corps, nor to the enlisted personnel of the army. We noticed, however, as with all voluntary measures, that there was great inequality in different garrisons, depending, of course, on the interest and enthusiasm or opposition of the commanding officer and the surgeon. Such conditions are inseparable from voluntary measures. In the department of the East, where the measure was actively pushed by the chief surgeon, Colonel John Van R. Hoff, more volunteers were obtained than in all other departments together. Lectures and missionary work among the officers were resorted to, as we early saw the truth of the well-known fact that the men follow cheerfully wherever the officers lead.

One commander[28] finding typhoid present in his garrison and epidemic in the neighborhood, succeeded in having the entire regiment vaccinated by refusing permission to leave the limits of the military post to anyone not protected against typhoid by vaccination or attack of the disease.

It is understood that in India volunteering was encouraged by refusing the opportunity, so dear to the soldier, of active service, to regiments whose quota of inoculated was small. Such incidents merely show the difficulty of protecting the health of a community which refuses to accept or to interest itself in measures for its own welfare.

In the English service, vaccination against typhoid has always been, and still remains, a voluntary measure; but we in March, 1911, introduced unequivocal compulsion on the occasion of the mobilization of a maneuver division in Texas.

In the army the duty of the physician is, of course, as in civil life, to treat the sick and minister to the wounded in the best and most approved manner; but the military surgeon has, beside, another duty, more important by far than the humanitarian one referred to: the duty of preserving the health of all under his charge and of having at all times the maximum number of able-bodied men on the firing line and of keeping them healthy enough to remain there. With this duty clearly before us, compulsory vaccination against typhoid was recommended for every person in the division not already protected by an authenticated attack of typhoid or by recent vaccination.

At this time we had already obtained records of vaccinations of approximately 20,000 persons, and knew that the preparation we were using was harmless; we knew too that it caused few severe reactions in healthy persons, and that no vaccination, however severe the immediate reaction may have been, had been followed by permanent injury to the individual; and further, that by all possible laboratory tests the immunity conferred was identical with and equal to that remaining after typhoid fever. Statistics of typhoid among vaccinated and unvaccinated troops were beginning to confirm, on a large scale, the laboratory tests.

It was impracticable from the data at hand to give accurate statistics comparing the rate among the vaccinated with the unvaccinated, but enough had been learned for our purpose. It was necessary to protect that body of 20,000 men against typhoid as well as against smallpox and other infections diseases. We were convinced that this could best be done if every man not already protected were vaccinated, and a recommendation to this effect from Surgeon-General George H. Torney was approved by the War Department, and vaccination was ordered on March 9, 1911, for all troops on the border.

[28] Lyster, Military Surgeon, 1911, xxviii, 528.

There is an apparent basis for objection to compulsory vaccination in typhoid fever, based on the reasons for universal vaccination against smallpox. In smallpox susceptibility is universal, and no other measure of sanitation or protection gives immunity. It is vaccination or nothing. With typhoid fever, under ordinary conditions, the problems presented are decidedly different. Not everyone is susceptible. During the Spanish-American War Reed, Vaughan, and Shakespeare[29] showed that one-fourth to one-third of those exposed contracted the disease.

Susceptibility to infection is, therefore, much less than with smallpox. Further, there are other good and practicable methods of prevention: pure water, good sewerage, and supervision of milk and other food supplies, properly carried out over a long series of years, will cause this disease to practically disappear, as it has in many parts of England and Prussia. This is well known, and is a condition we are looking forward to in our own country. Improved sanitation in the large cities is constantly reducing the typhoid death-rate, and under such circumstances neither compulsory nor voluntary vaccination need be considered. The conditions with which we have to deal in actual or mimic warfare are so entirely different that one can scarcely recognize the highly contagious disease which absolutely paralyzes regiments, divisions, and armies as of the same nature as the sporadic typhoid of cities. We cannot forget that typhoid fever is proteus-like in the variety of its disguises.

The following table shows the havoc wrought in some modern wars:

TABLE IV.

	Strength.	Typhoid cases.	Typhoid deaths.	Killed in action or died of wounds.	Died of disease.	Wounded.	Missing.
Franco-German War, German Army	....	73,393	6965	28,269	15,240	68,498	12,854
Spanish-American War, American Army	107,973	20,738	1580	243	2,565	1,445	....
Boer War, British Army	380,605	57,684	8022	7,702	13,250	22,829	....
Russo-Japanese War, Russian Army	....	17,033	....	34,000	9,300	141,800	....

We can all remember the experience of 1898 in military camps; it is well to review a few of the points brought out so clearly by Reed, Vaughan, and Shakespeare[30] lest we forget the lessions of experience. They found that typhoid fever appeared in over 90 per cent. of volunteer regiments within eight weeks of going into camp, and in some regiments of regular troops it appeared

[29] Abstract of Report on the Origin and Spread of Typhoid Fever in United States Military Camps during the Spanish-American War of 1898, Washington, Government Printing Office, 1900, p. 191.

[30] Ibid.

in three to five weeks; it also appeared both in small and large encampments in the Northern as well as in the Southern States. They stated their belief that "with typhoid fever as widely disseminated as it is in this country the chances are that if a regiment of 1300 men should be assembled in any section and kept in a camp the sanitary conditions of which were perfect, one or more cases of typhoid would develop."

They observe that typhoid fever is more likely to become epidemic in camps than in civil life because of the greater difficulty of disposing of the excretions of the human body. A man infected with typhoid fever may scatter the infection in every latrine in his camp before the disease is recognized in himself.

They demonstrated that water was not an important cause of the spread of the disease and that flies undoubtedly served as carriers of the infection; that the spread was through contact and was characterized by a series of company epidemics, each having more or less perfectly its own individual characteristics.

They showed that an organization once infected continued to produce new cases, even though it changed its camp site or travelled long distances by land or by sea. This doctrine, radical at the time, has since been made simple through the discovery of temporary and chronic bacillus carriers.

In this war the mortality from typhoid fever was 86.24 per cent. of the total. The morbidity was 192.65 per thousand of mean strength, or a little less than one-fifth. The mortality per thousand of mean strength was 14.63.

When orders were suddenly issued early in 1911 for the mobilization in Texas, California, and along the Mexican frontier of the largest body of troops in the field since the Spanish War, the question of typhoid prophylaxis ceased to be academic and became a practical question insistant on solution. The mobilization plans did not provide for fixed camps, where water supplies and even sewerage systems might have been arranged, but called for active service in the field, under conditions simulating, as closely as possible, actual warfare. Indeed, we did not know but that a campaign into Mexico might not follow quickly the assembling of the troops. Even the incinerators recently used in maneuver camps for the destruction of excreta by fire were forbidden, as being too heavy and cumbersome and too expensive to form part of the equipment of moving troops.

Experience during the Spanish-American War had taught what to expect in large and protracted camps. In eight weeks it was thought that through the agency of flies, dust, and the inevitable close contact of crowded camps and more crowded tents there would be some cases of typhoid, and that probably the advances in field sanitation could be relied upon to protect against a repetition of that war's disasters. Although conditions could not have been

expected to have been as bad as in 1898, there would likely have been typhoid fever enough to have handicapped some portion of our small force had an advance across the border become necessary.

With these possibilities in view and with complete confidence in both the effectiveness and harmlessness of antityphoid vaccination, it can be understood why, in the opinion of the Surgeon-General, compulsory vaccination was to be preferred to the half-way measure of volunteering.

The results fully justified the position taken. The maneuver division, as it was called, was ordered to mobilize in Texas, California, and along the Mexican border in March, 1911. They remained in camp and on the border patrol for a period of four months, when the greater number were returned to their garrisons. A few thousand men had already received the prophylactic, and the others were vaccinated as rapidly as they arrived. The vaccine was prepared at the laboratory of the Army Medical School in Washington and shipped as rapidly as it could be used. During the thirty days after the receipt of orders, approximately 60,000 doses were prepared and delivered. As the full course of three doses occupies twenty days we had no great difficulty in supplying the vaccine as rapidly as it was needed.

In addition to the main divisional camp at San Antonio, smaller camps occupied by separate brigades were established at Galveston, Texas, and San Diego, California. At Galveston there were about 4500 persons, and at San Diego, 3000. No cases of typhoid were reported among the troops in Galveston, although the chief surgeon estimated that there were 192 cases among the civil population of the city during the period of the encampment. From San Diego only 2 cases[31] were reported, and 1 of these was doubtful. Other detachments, smaller in size, were scattered along the border, yet there was no typhoid. The camp in San Antonio was the largest and best known of the maneuver camps, and the interest of the public has centred upon it. For a period of four months, beginning in March, 1911, almost 13,000 troops were located there, and anyone who visited it knows that all the elements which tend to affect the health of men under canvas were controlled better than they had ever been before. The sanitary difficulties of camp life arise mainly from the lack of established water, sewer, and scavenger systems, and these difficulties were overcome at San Antonio by new and ingenious, yet practical, expedients. Flies, the cause of so much trouble in 1898, were kept down to a minimum by a series of simple yet effective company crematories. In drawing a mental picture of a military camp, one is quite apt to overlook the necessary camp animals. At San Antonio, for instance, there were 6000 horses and mules scattered here and there in close proxi-

[31] Annual Report of Surgeon-General of United States Army, 1912, p. 51.

mity to the quarters of the men, and the proper disposal of the stable refuse by fire was in itself no small undertaking.

One can best judge of the combined effects of vaccination and sanitation by comparing this camp with the one located at Jacksonville in 1898.[32]

TABLE V.

Number of troops	Cases of typhoid certain.	Certain and probable.	Deaths from typhoid.	All deaths
1898, Spanish-American War, Camp at Jacksonville, Florida.				
10,759	1,729	2,693	248	281
1911, Camp at San Antonio, Texas.				
12,801	2	....	..	11

At Jacksonville there were assembled 10,759 men, among whom there were 1729 undoubted cases of typhoid, and including those in which a diagnosis of typhoid was probable there were 2673 cases, with 248 deaths. This camp lasted approximately as long as the camp at San Antonio in 1911; both camps were situated in about the same latitude, and each had artesian well water of excellent quality, yet in 1898 there were over 2500 cases of typhoid fever, with 248 deaths, and in 1911 only 2 cases, with no fatalities.[33] We know that the immunity was not due to lack of exposure, since there were reported to the health office 49 cases of typhoid fever, with 19 deaths, among the civil population of the city of San Antonio during the period of encampment.

Our men were not rigidly confined to camp, but had leisure and opportunity to visit the neighboring cities of San Antonio and Galveston. Thousands of soldiers spent more or less time in these cities, where they ate, drank, and slept; in fact, became for the time being a part of the community. In Galveston especially, where a ten-minute ride carried one from camp to the heart of the city, the number of men visiting town was large. The soldier is not overparticular where he obtains food and drink: restaurants, good and bad, lunch wagons, street-corner stands, all have his patronage. Fruits and pastry and sweets were purchased of hucksters lined up along the camp boundaries. The best kind of camp sanitation alone could not have prevented typhoid in the presence of all these possible chances of infection, with the disease as prevalent as it was in the adjoining cities. What it did do was to reduce the number of chances of infection and prevent the appearance of secondary cases from the two which actually occurred.

[32] Kean, Jour. Amer. Med. Assoc., 1911, lvii, 713.

[33] Annual Report of Surgeon-General of United States Army, 112, p. 51.

Many other striking illustrations of the efficacy of vaccination might be instanced; one, however, must suffice:[34] A cavalry regiment of about seven hundred men engaged in a twenty-one-day practice march through a part of Tennessee, where typhoid fever is endemic throughout the year. During their march of six hundred miles there was no attempt to boil or sterilize the drinking water. The amount of sickness was practically *nil*, and no cases of typhoid developed. Following a previous practice march in the same region ten cases occurred, and the further spread of the disease at that time was finally stopped by wholesale vaccination.

Compulsory vaccination in the Southern maneuver camps was ordered on March 9, 1911; the next step, June 9, 1911, was the extension of the order to all recruits; since which time 2000 to 3000 recruits have received the prophylactic treatment each month, at the same time being vaccinated against smallpox. If the vaccinia be severe the second dose of the typhoid prophylactic is postponed a few days, but in no other way has it been necessary to deviate from this routine of simultaneous vaccination against the two diseases. The two vaccinations are completed by the time the man has been twenty days in the service. It is our present practice to revaccinate against both smallpox and typhoid at the beginning of each four-year period of enlistment. This is not because the immunity has by that time disappeared, for its duration is not yet known. It no doubt diminishes gradually, as in the case of smallpox, yet in the service it is desirable to maintain the army in a maximum state of protection against infection at all times, and it does not seem advisable to omit vaccination until an outbreak of typhoid shows the disappearance of all immunity. Smallpox has been almost entirely suppressed; there were only 5 cases among American troops in 1911, with no fatalities, and typhoid has ceased to be the scourge of former days.

The next and most important step was the extension of compulsory prophylaxis to all persons in the service under forty-five years of age; this was ordered September 30, 1911. In the United States proper the order was not fully executed before January 1, 1912. In the Philippines it was not carried out until the first part of 1913.

If vaccination gives the protection we believe, its good effect should show in the total number of cases reported in the army year by year, and the following table and charts have been arranged to show these facts:

[34] Lyster, Military Surgeon, 1911, xxviii, 528.

TABLE VIII.—Typhoid Fever (United States), among Enlisted American Troops.

Year.	Mean strength.	Absolute cases.	Number deaths.	To each 1000 soldiers of the command the ratios are: For cases.	For deaths.
1901	26,515	250	17	9.43	.64
1902	39,736	341	34	8.58	.86
1903	42,264	246	12	5.82	.28
1904	43,940	247	12	5.62	.27
1905	42,834	153	13	3.57	.30
1906	40,621	230	12	5.66	.28
1907	35,132	124	7	3.53	.19
1908	46,316	136	11	2.94	.23
1909	57,124	173	16	3.03	.28
1910	55,680	129	9	2.32	.16
1911	55,240	44	6	0.80	.11
1912	58,119	15	2	0.26	.03

NOTE.—This includes all information available in the Surgeon-General's Office to April 1, 1913. Strength for officers and enlisted men for 1912 is only approximate, as it was not possible to obtain a true strength on that date.

TABLE IX.—Showing the Number and Proportion of Typhoid Fever Cases Contracted before Enlistment and among the Protected (United States Proper only) Officers and Enlisted Men.

Year.	Total cases.	Total deaths.	Infected prior to enlistment.	Among the vaccinated. Number of cases.	Number of deaths.
1909	173	16	?	1	0
1910	129	9	?	4	0
1911	44	6	?	7	0
1912	18	3	5	6	0

TABLE X.—Typhoid Fever, 1901 to 1912, for the Whole Army, Officers and Enlisted Men, at Home and Abroad.

		Cases.		Deaths.			Occurring among those who were vaccinated.	
Year.	Mean strength.	No.	Ratio per 1000 of mean strength.	No.	Ratio per 1000 of mean strength.	Percentage of total cases.	Cases.	Deaths.
1901	81,885	552	6.74	74	.88	13.0		
1902	80,778	565	6.74	69	.85	12.2		
1903	67,643	348	5.14	30	.44	8.6		
1904	67,311	293	4.35	23	.33	7.8		
1905	65,688	206	3.14	20	.30	9.7		
1906	65,159	373	5.72	18	.27	4.8		
1907	62,523	237	3.79	19	.30	8.0		
1908	74,692	239	3.20	24	.31	10.0		
1909	84,077	282	3.35	22	.26	7.8	1	0
1910	81,434	198	2.43	14	.17	7.1	7	0
1911	82,802	70	.85	8	.10	11.4	11	1
1912	88,478	27	.31	4	.044	14.8	8	0

From these figures and charts the deductions would seem quite clear. They are based upon accurate observations of from 70,000 to 80,000 men each year, and are as accurate as only great care can make them. We see a sudden drop in both morbidity and mortality

during the last two years, which corresponds with the increase in the use of a prophylactic immunization during the same period.

During the year 1913 there have been no cases of typhoid fever reported up to October 1, and in order to compare it with previous years the following table has been prepared, which shows the total number of cases for the last six years, for the first three-quarters of each year. From this it is apparent that the beneficial effects of vaccination are much greater than previous experience would lead one to believe.

TABLE XI.—Typhoid Fever. United States Officers and Enlisted Men, United States Army.

	Year.	Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Total for 9 mos.
Voluntary	1908	5	6	4	2	3	11	14	31	25	26	12	8	101
	1909	4	10	6	4	11	15	26	14	16	45	20	6	106
	1910	8	11	1	4	2	6	12	27	21	16	20	11	92
	1911	3	3	3	7	4	4	4	7	4	4	1	0	39
Compulsory	1912	1	2	2	0	0	3	1	3	1	4	0	1	13
	1913	0	0	0	0	0	0	0	0	0				0

Paratyphoid fever included in figures for 1908, but excluded in other years.
Cases paratyphoid: 1909, 3; 1910, 3; 1911, 2; 1912, 3; 1913, 0.

Since the Spanish-American War, medical officers of the army have given much attention to the prevention of this disease, and have greatly reduced the frequency of its occurrence. The greatest care, however, in sanitation and hygiene did not appear to be successful in reducing the number of cases much below 150 per annum in the United States for the present strength of the army, or an average number of not quite 3 cases to every 1000 men.

The importance, for statistical purposes, of the year 1912 arises, as may be noted, from the fact that not until then were there complete statistics for a calendar year, covering compulsory immunization of the entire army. All previous tables were based upon either voluntary immunization of small numbers or mixed voluntary and compulsory immunization, and such tables were always open to the objection that volunteers constitute a group of thoughtful, careful men, who would naturally be less liable to infection than the rank and file of the army. This objection is disposed of by the compulsory use of typhoid prophylactic, and the year 1912 demonstrates fully what may be accomplished when the measure is used fearlessly and regularly upon a large number of persons.

In the navy[35] "the compulsory use of typhoid prophylactic was inaugurated on January 1, 1912, and the inoculation of practically the entire naval personnel has been completed without a single serious result or casualty. Only a small fraction of 1 per cent. had reactions necessitating rest in bed, and but a small percentage of individuals required to be excused from duty. As this policy has

[35] Annual Report of Surgeon-General of United States Navy, 1912, p. 16.

been put into effect so recently, it is impracticable to formulate any comparative date relative to the rate of the disease, but reports, made in response to a bureau circular letter, show that in men who had received the three injections only one authentic case of typhoid fever has occurred, although three were reported as such in which laboratory findings failed to verify the diagnosis. One mild case occurred in a man who had but two inoculations. One officer, known to be a typhoid carrier, was found to be free of the typhoid bacillus subsequent to receiving the three injections required. The prophylactic administered to the personnel on the Asiatic station was prepared at the Naval Hospital, Canacao, Philippine Islands."

All other antityphoid vaccine used by the navy was prepared in our laboratories at the Army Medical School.

The following table shows the amounts of vaccine furnished from the Army Medical School for the use of the army, navy, militia, and others.

TABLE XII.

Year.	Army.	Navy.	Militia.	Others.	Total.
1909	6,000 c.c.	....	....	1,000 c.c.	7,000 c.c.
1910	68,592 c.c.	....	....	7,251 c.c.	75,843 c.c.
1911	237,540 c.c.	50,000 c.c.	22,241 c.c.	6,692 c.c.	316,473 c.c.
1912	147,463 c.c.	187,284 c.c.	28,751 c.c.	11,218 c.c.	374,716 c.c.
	495,595 c.c.	237,284 c.c.	50,992 c.c.	26,161 c.c.	774,032 c.c.

ESSENTIALS FOR A TYPHOID VACCINE. The essential requirements for a prophylactic vaccine are that the immunization shall be harmless, that the process shall not be attended with unpleasant symptoms, and that the immunity shall be reasonably long.

In addition, the vaccine to be of real service must be available in ample quantity at short notice, which means, of course, that the vaccine must either be stable enough to withstand long storage or that the method of preparation be so simple that unlimited quantities will be available on short notice for use in epidemics and among troops upon mobilization.

That the immunization is harmless is sufficiently clear, since about 200,000 men, as nearly as can be estimated, have already been immunized with our vaccine without a single fatality or serious complication.

At San Antonio 1 case of musculospiral neuritis was apparently directly due to the vaccination. Our directions distinctly call for a subcutaneous inoculation, as slow rather than rapid absorption is desired; yet some physicians persist in giving deep hypodermics, as was evidently done in this case.

At Guantanamo, Cuba, in 1911, 1 case occurred which has aroused some comment.[36] A private of the marine corps received

[36] United States Naval Bulletin, 1911, v. 336. Freeman, Southern Med. Jour., 1912, v. 4.

one dose of vaccine. He felt perfectly well at the time and previous to the inoculation. Two days later he was admitted to the hospital, acutely ill with high fever (104.6°), headache, and dulled intellect. Within twenty-four hours after admission he began to grow rapidly worse. He died seventy-six hours after admission and seven days after vaccination. The autopsy record and examination of the ileum, preserved at the Naval Medical School, show clearly that the man at the time of his death was at the end of the second or beginning of the third week of the disease. His infection was, therefore, at least a week old when the single dose of vaccine was given. Whether or not it affected his condition it is impossible to say. Certainly, one is not justified in drawing any inference as to the harmful effects of vaccination from a single case, and that an ambulatory one, since walking cases are notorious for the late intensity of symptoms and high mortality.

It is not unusual to read in public prints of fatalities following vaccinia, and a recent instance, reported by Broeckerhoff,[37] is quite comparable to the Guantanamo case. A nine-year-old boy was vaccinated against smallpox on May 7; at the time he fainted and was sent home in the company of some other boys. On arrival he was pale, and complained of pains and headache, and went to bed immediately. The physician who saw him reported the vomiting of blood and the presence of dark blood in the stools. There was no appreciable rise of temperature, and the pulse was small and rapid. There was no morbid change at the site of vaccination. On May 9 he died, without developing any new symptoms. The autopsy showed definitely that the cause of death was hemorrhage from typhoid ulcers, and that the vaccinia was in no way responsible for his death.

In this connection it is necessary to remember that we never administer the prophylactic to any but the healthy. If there be any doubt about possible illness the treatment is postponed until a diagnosis can be made.

We also know that, except in rare instances, the immunization is not attended with unpleasant symptoms. When the practice was first introduced, careful records of all general reactions were kept, and the following table shows the rarity of severe general reactions; in over 97 per cent. of persons the general reaction was mild or absent.

TABLE XIII.—Showing Degree of Severity of General Reactions.

Dose.	Number of doses.	Per cent. absent.	Per cent. mild.	Per cent. moderate.	Per cent. severe.
First dose	45,680	68.2	28.9	2.4	0.3
Second dose	44,321	71.3	25.7	2.6	0.2
Third dose	38,902	78.0	20.3	1.5	0.1
	128,903				

[37] Centralblatt f. Bakteriol., 1912, 1 Abt. Ref., lv, 549.

Severe reactions occurred in only one to three persons per thousand, and the experience of the navy using our vaccine is confirmatory of our own.

The degree of immunity is, of course, not absolute, since 27 cases (including 8 so far reported for 1912), with 1 death from hemorrhage, have been reported during the past four years.

In the light of our experience with vaccinia it is improbable that we shall ever obtain an immunization process which will give absolute immunity. There is an individual variation among persons just as among animals. In the laboratory it is not unusual to find certain animals refractory to immunization, and we cannot expect more uniformity among human beings.

The army is as well protected against smallpox as repeated vaccination can make it, yet we had in the entire army, American and native troops, 21 cases in 1908, 7 in 1909, 17 in 1910, and 20 in 1911, a total of 65 cases, with 2 deaths in four years, against 27 cases of typhoid fever, with 1 death, after antityphoid vaccination in an equal length of time.

The duration of the immunity following our method of prophylaxis has not yet been determined. The interval between vaccination and the onset of typhoid fever in the 27 cases referred to is as follows:

TABLE XIV.

Case.	Date.	Patient.	Interval.	Station.
1	Aug. 2, 1909	R. J.	6 days after 2d dose	Transport
2	Mar. 6, 1910	A. T.	9 months after 2d dose	Philippine Islands
3	June 7, 1910	A. S.	1 month after 3d dose	Fort Mott, N. J.
4	July 24, 1910	R. J. S.	4½ months after 3d dose	Philippine Islands
5	Aug. 5, 1910	E. L.	3½ months after 3d dose	Fort Benj. Harrison, Ind.
6	Aug. 5, 1910	B. F. H.	1 month after 3d dose	Fort Washington, Md.
7	Aug. 7, 1910	S. P.	2 month after 3d dose	Fort Washington, Md.
8	Dec. 20, 1910	H. D. C.	4 months after 3d dose	Philippine Islands
9	Jan. 12, 1911	J. B.	9 months after 3d dose	?
10	May 12, 1911	R. K.	5 days after 3d dose	Point Loma, Cal.[33]
11	May 9, 1911	J. D.	21 days after 3d dose	San Antonio, Texis
12	June 12, 1911	R. C. K.	.....	Point Loma, Cal.
13	July 10, 1911	G. M.	.....	San Antonio, Texas
14	Sept. 25, 1911	F. H. S.	3 months after 3d dose	Fort Sam Houston, Texas
15	Oct. 13, 1911	H. K. M.	6½ months after 2d dose	Fort Sam Houston, Texas
16	Oct. 13, 1911	E. W.	.....	Fort Sam Houston, Texas
17	June 1, 1911	A. P. B.	7 months after 3d dose	Japan
18	Nov. 26, 1911	F. J. T.	20 months after 3d dose	Philippine Islands
19	Dec. 28, 1911	J. C.	6 months after 3d dose	Porto Rico
20	Jan. 28, 1912	W. C. E.	21 days after 3d dose	Fort Slocum, N. Y.
21	June 4, 1912	J. G. K.	4 months after 3d dose	Field, Cal.
22	Aug. 3, 1912	H. S. D.	12 months after 3d dose	Fort Williams, Me.
23	Aug. 30, 1912	W. McC.	17 months after 3d dose	Fort Oglethorpe, Ga.
24	Oct. 15, 1912	A. E. S.	21 months after 3d dose	Fort Leavenworth, Kan.
25	Oct. 18, 1912	A. J. B.	13 months after 3d dose	Washington, D. C.
26	April 15, 1912	F .F.	4 months after 3d dose	Schofield Barracks, H. T.
27	Aug. 16, 1912	M. C. (P. S.)	8½ months after 3d dose	Philippine Islands

[33] History of Typhoid in 1905.

In only 4 instances in the 27 reported cases was the interval between vaccination and infection less than one month; should anyone feel inclined to interpret these infections as instances of a negative phase, they would also serve to illustrate its rarity.

Within three months after vaccination there were 8 cases.

Within six months and over three months there were 6 cases.

Within twelve months and over six months there were 6 cases.

Within eighteen months and over twelve months there were 2 cases.

Within twenty-four months and over eighteen months there were 2 cases.

Interval unknown, 3 cases.

It is evidently impossible from this small collection of cases occurring in the military service to draw any conclusions as to the duration of the immunity.

The experience of the English Army in India shows[39] that the immunity begins to fall after two and a half years. This, however, does not assist us greatly, since the difference in the preparation of the vaccine and our use of three doses to the English two leads us to hope for a greater degree and longer duration of the immunity. That there is some justification for this expectation can be shown by comparing the results obtained among English troops in India in 1911[40] with those obtained in the entire American Army at home and abroad for the same year.

TABLE XV.—Typhoid Fever, 1911.

	Total strength.	Absolute numbers. Cases.	Deaths.	In vaccinated persons. Cases.	Deaths.
English troops in India	72,371	170	22	106	11
Entire American Army	82,802	70	8	11	1

RATIOS.

	Admissions per 1000.	Deaths per 1000.	Case mortality.
India	2.3	0.3	12 9 per cent.
United States and colonies	0.85	0.1	11.4 per cent.

In considering this table one should, of course, remember that typhoid is a much more common disease in India than in either the United States or its colonies, and the chances of infection are therefore greater. Vaccination has also been used in India since 1904, and it is possible that the interval between vaccination and infection may in some cases have been a long one. It is probable, nevertheless, that our agar vaccine and the use of three doses rather than two are the main factors in producing better results in our service.

[39] Firth, Jour. Royal Army Med. Corps, 1911, xvi, 589.

[40] Report of Health of Army for 1911, London, 1912, liii, 37.

The old idea that the protective power of the vaccine lasted only so long as agglutinins and other antibodies were demonstrable in the serum has been largely discredited, since we know that agglutinins, at least, are present in the serum of vaccinated persons generally as long as they are demonstrable in persons who have had typhoid, and who are, as a rule, immune for life.

Further essentials of a good vaccine are that it be available in ample quantity at short notice; that it be stable enough to be stored for at least three months, and to be shipped about the country for use by any physician. These requirements rule out the greater number of the vaccines proposed. It is possible, in fact probable, that the future will give us better vaccines than we now use, yet no vaccine can be seriously considered which does not fulfil these conditions.

The principal modifications suggested in late years are those of Vincent, of the French Army, and Metchnikoff and Besredka.

Vincent's[41] vaccine is made as follows: several strains isolated in the neighborhood in which the vaccine is to be used are grown on agar twenty-four to forty-eight hours; the growth is taken up in salt solution and kept at 37° C. from two to four days; after centrifugation the supernatant fluid is sterilized by being shaken with ether, which is then allowed to evaporate. Three or four injections are given at short intervals.

Vincent reports the following results from Algeria:

2632 not vaccinated	171 cases	64 per 1000
129 vaccine of Wright	1 case	7 per 1000
81 vaccine bacillary polyvalent	0 cases	0 per 1000
73 autolysate polyvalent	0 cases	0 per 1000

These and other results so far reported by Vincent are excellent, and, thanks to his work, opposition is rapidly disappearing in France, and vaccination is now being used to some extent in the army and navy. We have had no personal experience with it.

Metchnikoff and Besredka[42] have conducted the most extensive investigation of recent years, using chimpanzees as test animals. They found that in these animals killed vaccines were powerless to prevent typhoid fever when overwhelming doses of infectious material were used, but that prophylactic immunization with sensitized living bacilli gave them power to resist even large doses, such as may occur in milk-borne epidemics. Interesting and valuable as this work of Metchnikoff and Besredka undoubtedly is, it nevertheless deals with a limited number of apes, and for practical purposes cannot, in the opinion of the writer, be compared to the work in the military service with nearly 200,000 human beings.

[41] Compt. Rend. de l'Acad. Sci., February 7 and 21, 1910; Compt. Rend. de la Soc. de Biol., July 29, 1911; Bull. de l'Acad. de Méd., 1910, xl, 226; Ibid., 1911, iv, 63.

[42] Ann. de l'Inst. Pasteur, 1911, xxv, 193.

It is evident from Tables VIII and X and Charts I and II that our present vaccine is conferring immunity in as great a degree as has ever been done by any vaccine. It is certain that in the military service, typhoid prophylaxis is quite as successful as vaccination against small-pox, our old ideal of what a prophylactic measure

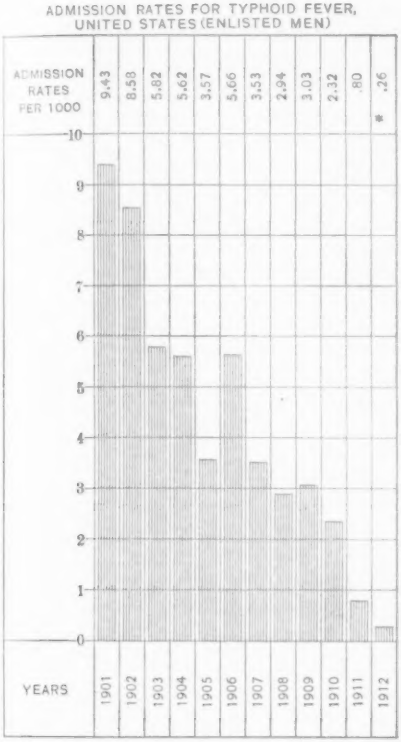


CHART 1.

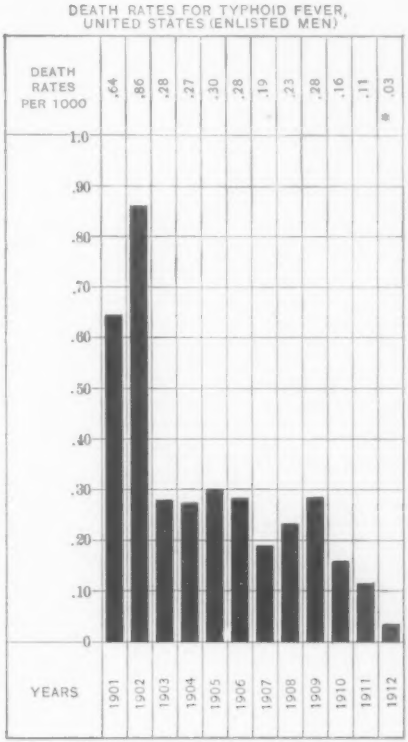


CHART 2.

* All information available in the Surgeon-General's Office January 10, 1913. Later reports may show additional cases. Strength only approximate, as it was not possible to obtain a true strength on January 10, 1913. Antityphoid vaccination, begun voluntarily in 1909, was made compulsory in 1911.

should accomplish. It is evident from this that the opinion held by many scientists that living vaccines and viruses are superior to dead vaccines, and that a high degree of immunity can only be conferred by the use of living vaccines, must be reconsidered at least so far as typhoid fever and smallpox are concerned; our experience has definitely demonstrated that the immunity conferred by dead typhoid bacilli is in no way inferior to the immunity against smallpox conferred by living vaccine virus.

Excellent as the living, sensitized vaccine of Metchnikoff undoubtedly is, there are at the present time certain insuperable objections to its use in our service; it consists of living bacteria, and is not stable and cannot be stored even for short periods. Although it appears to be safe to inject attenuated vaccines subcutaneously, it is still a question whether they could be handled safely and might not accidently infect persons by the mouth. Another objection is the possibility of contamination. This is not theoretical, as it has occurred twice in the history of cholera vaccination, with disastrous effects upon the progress of the movement. Contamination of a killed vaccine can be absolutely ruled out at the time of its preparation, and enough antiseptic can be added without damage, to prevent further accidental contamination. Living vaccines can never be made and handled with the same confidence, and this circumstance remains a serious objection to the use of such vaccines on a large scale.

There is another point of equal if not greater importance. We in the army and navy have come to rely upon universal compulsory vaccination. Does anyone imagine that the time is ripe for any physician to recommend, or for cabinet members to order, every man in the service to submit to vaccination with living typhoid bacilli? From conversations with persons in authority the idea has been firmly impressed upon the writer that the time for that has not yet arrived.

Would it be possible to achieve the same good results by voluntary vaccination with a living vaccine of equal protective power? How many would volunteer for vaccination under such circumstances? Certainly no more than at present. In the English Army in India, after eight years of success and hard work, 85 per cent. of the men are vaccinated, and it seems improbable that this percentage can be appreciably increased. We have learned by experience that typhoid searches out and often finds the unvaccinated man: 12 out of 18 cases in 1912 and 37 out of 44 in 1911 were among the uninoculated portion of our army. It seems, therefore, probable that greater good will be accomplished by the compulsory use of an admittedly safe vaccine than by the voluntary use of a living prophylactic.

Our experience since 1909 has left no doubt about the success of antityphoid vaccination in the army and navy. The measure has come to stay. Is it not, however, desirable under other circumstances as well? On certain points there is a pretty general agreement. Most physicians believe that the personnel of hospitals and dispensaries should be protected, since experience has shown an unduly high rate among internes, nurses, and attendants. Hachtel and Stoner[43] state that in six Baltimore hospitals the

[43] Amer. Jour. Public Health, ii, 157.

incidence among nurses and attendants over a period of five years was twelve to twenty times greater than the rate for the city. Joslin and Overlander[44] found the rate among nurses in Boston was 161 per 10,000 of population as compared with twenty for the State of Massachusetts, or eight times as high.

We should, however, go a little farther than this and vaccinate all who in any way come in contact with the sick, including the family and servants in contact with typhoid fever cases.

There are many other groups of persons to be vaccinated about which there is no dispute, such as those who live in industrial villages, mining towns, and isolated and temporary asylums, and especially schools.

In lumber camps, the camps of engineers, contractors, and pleasure-seekers the use of the typhoid prophylactic will richly repay the time and trouble necessary for its administration.

Its use, however, is not limited to these classes of persons. The typhoid death-rates for New York, Boston, Chicago, and most other large cities in the North are low, ranging from 4.7 in Bridgeport to 17.5 in Philadelphia in 1910, and so long as the inhabitants of these cities remain at home they run little danger of contracting the disease. Remaining at home, however, is a thing most of us are not accustomed to do; we send our patients and our families, and go ourselves to the country, seaside, and mountains, where the typhoid-rate may be many times as high as at home. Such terms as vacation typhoid and travel typhoid are common expressions, and show the danger to which we are constantly exposed. A technical term of importance in this connection is residual typhoid, that is, the typhoid which remains in a community after pure water and good sewerage have been introduced. This is the typhoid we have been fighting in army posts the past few years; it is the typhoid which remains in New York, Washington, and Richmond after these cities have been furnished with pure water. It is due to many factors: milk, flies, contaminated foods, contact with chronic and temporary carriers, and with typhoid cases. Shall nothing be done to reduce the typhoid fever which remains after pure sanitation has done its best? We know from army experience that vaccination will reduce it surely and without danger.

Leaving the subject of residual typhoid in sanitary areas, let us consider the chances of infection in unsanitary regions, either urban or country. Here we know the chances of infection are much greater; we all know how common typhoid is in this country every summer and autumn. Osler says (*Principles and Practice of Medicine*): "From 1900 to 1909 the death-rate in the registration areas was 29.5 per 100,000. It is estimated that from 35,000 to 40,000 persons die from typhoid fever every year, so that at a moderate

[44] Boston Med. and Surg. Jour., 1907, clvii, 247.

estimate nearly 500,000 people are attacked annually. It is more prevalent in country districts than in cities, and, as Fulton has shown, the propagation is largely from the country to the town."

The last census bulletin covers the year 1910, and it shows considerable improvement, the death-rate being 23.5 per 100,000. It is only in half a dozen eastern cities that our typhoid rates approach the low rates of the leading cities of western Europe, so that we have still much to do before the typhoid situation is at all satisfactory. Each year shows some improvement, as one community after another wakes up to the fact that investments in sanitation pay better interest than gold mines; nevertheless, improvements come at a snail's pace, and many generations must elapse before this country can equal England and north Germany in its freedom from typhoid. It is admitted that sanitary administration in this country has no organization; there is no national authority with power to compel obedience; even the States show no uniformity in their powers or standards. In this matter of sanitary administration we see the doctrine of home rule carried to the limit of absurdity. What can be done to protect against typhoid until such time as the Nation, the State, and our own communities shall give proper attention to sanitary problems, and guarantee to all that inalienable right the pursuit of health and happiness, free from the dangers of preventable disease. To illustrate our present dangers, one example will serve as well as another. Lumsden[45] has reported an outbreak of gastro-enteritis and typhoid among the passengers of a Mississippi river steamer. On July 29, 1912, about 1500 persons went on a Sunday school excursion. The day was warm, the steamer's water tanks small, and, to supply the demand, must often have been refilled from the river. Within a short time no less than 600 became ill of gastro-enteritis, and 13 cases of typhoid, with 3 deaths, were traced by Lumsden. As the disease was not reportable in either Iowa or Illinois, where this occurred, he felt certain that all had not been recorded.

This may serve to remind us that, at the present time, sanitation alone is not ample protection, and that some measure of personal prophylaxis is absolutely essential the moment we leave home. We are then reduced to measures of personal hygiene and individual prophylaxis, and the best method at the present time is vaccination. Only by it can we protect ourselves against infection with as great certainty as against smallpox; in this day and generation it is, in fact, the one promising method of protection from the sporadic and residual typhoid which has so far resisted the efforts of sanitarians. There is no occasion for conflict between the advocates of general and individual prophylaxis; one is as necessary as the

[45] Public Health Reports, Washington, 1912, xxvii, 1960.

Cutaneous Lesions on the Right Hand in a Fatal Case of Streptococcus Septicemia.

other, and no one interested in the suppression of this disease can afford to ignore either.

All sound thinking people look forward to the time when National, State, and local health authorities will unite in a concerted movement for better sanitary conditions; unite in the fight against infectious diseases; when they will advance together along broad lines in the suppression of this scourge of civilization. In this campaign, antityphoid vaccination, as well as sanitation can, the writer feels sure, be counted upon to play a leading role.

CUTANEOUS MANIFESTATIONS OF SEPTICEMIA

By John W. Churchman, M.D.,
Assistant Professor of Surgery in Yale University.

(From the Continuous Surgical Service, the New Haven Hospital.)

Despite the completeness of our knowledge of infection, there are a number of facts about the invasion of the body with microörganisms which defy explanation. Especially is this true of the selection of certain organs by one infective agent and their immunity from another. The susceptibility of the urethral mucosa to the gonococcus and the almost complete immunity of the vesical mucosa are well-known examples of this selective action. A similarly familiar instance is furnished by tuberculosis and syphilis of the genitalia, the affinity of the former for the epididymis, and the latter for the testicle being quite unexplained. A more striking instance still is the apparently absolute immunity of the prostate to syphilis; for though this disease may attack most of the tissues and organs in the body, no authentic instance of syphilitic prostatitis is on record, and the few reported cases in the literature will not bear scrutiny. A similar selective affinity is also exhibited by neoplasms. The female breast, so often the site of newgrowths, is almost immune to one of the commonest forms of neoplasm, the lipoma. In the rectum and pelvic colon, carcinoma is a frequent disease; yet in the adjacent hepatic flexure it is relatively rare. Whatever the explanation of these facts and others like them may be, it is certain that we must seek further than an irrelevant anatomical fact, like "a richer blood supply" or a "poorer blood supply," to account for them. Recent observations with the aniline dyes have shown how extraordinarily sensitive selective actions may be, and have suggested that chemotropism may play a part in the apparent vagaries of infection.

The pyogenic organisms, though fairly impartial in their ravages,

may in an individual case exhibit a choice of lodgment and symptoms out of the ordinary. These unusual symptoms are sometimes to be ascribed to known peculiarities of the invading organisms themselves. The phenomena, for instance, of streptococcic septicemia are not in general identical with those of staphylococcic septicemia; and an organism like Bacillus aërogenes capsulatus produces a septicemia which has features peculiar to itself. It seems not unlikely that Bacillus mucosus capsulatus tends to produce a septicemia of the hemorrhagic type; at least a number of observations of this kind are on record.

One of the unusual lesions of pyogenic septicemia, odd both in character and in site, was illustrated by a case of streptococcic septicemia which I saw a year ago in the New Haven Hospital. In this instance the lesions were unique in my experience. The patient, a Pole, aged fifty-nine years, had been struck on the head with a brick one week before admission, receiving a ragged laceration on the scalp in the right frontal region, near the hair line. The wound had been sutured by a physician. The patient had then gone on a week's drunk, and when next seen by his physician was found to be running a temperature of 102.5, and was sent to the hospital. On admission the edges of the scalp wound were found to be separated by necrotic tissue and the skull could be easily explored with the finger. No fracture was present. There was impaired resonance throughout the right back of the chest and the axilla, and coarse musical rales were heard throughout the right side. The temperature ranged around 102; muttering delirium soon developed, and a consolidation of the whole right lung was evident on the day following admission. The most striking feature, however, was the rapid development of the cutaneous lesions described below. Streptococcus pyogenes was isolated in pure culture from the blood and also from the fluid aspirated from the vesicle on the right little finger. The patient died from a streptococcic septicemia and double pneumonia seventy-two hours after admission.

The cutaneous lesions in this case are well represented in the accompanying illustration. For economy of space all the lesions are drawn on the same hand, though one was situated on the left hand. Scattered vesicles similar but less striking were also present on the feet. The rapidity of development of these lesions was a striking feature. The lesion on the little finger was found at rounds in the morning, though there had been no signs of it the night before. It seems probable that the lesions illustrated represent the evolution of the condition, and that it began as a bleb with a hyperemic base, containing clear fluid. The contents soon became blood-tinged, and finally (the whole process occupying but a few hours) a bulla filled with deep blue fluid resulted, as shown on the little finger in the drawing. This fluid lay between epidermis and dermis. The appearance was that of a thin finger-cot stretched

over the finger and distended with a blue fluid which could be seen shimmering through. The sharp edge of the lesion, with perfectly normal skin beyond, is shown in the illustration, and this feature has not been exaggerated by the artist. The lesion was an entirely intracutaneous one; there was no gangrene of the soft parts of the finger. Pure culture of Streptococcus pyogenes was obtained from fluid aspirated from the lesion.

The most familiar cutaneous manifestations of invasion of the body by microörganisms are the syphilides and (if a micro-organism be conceded in this case) the exanthemas. In the class of diseases more strictly known as septicemia the following groups of cutaneous phenomena are to be distinguished:

1. *The Erythema Group.* Here are included the erythematous patches sometimes seen in the neighborhood of an infected joint or over an infected muscle. More striking is the "surgical scarlet fever" of Paget, Dieulafoy, Billroth, and others. In this condition a scarlet erythema, often fleeting but sometimes persistent, appears on the body following an operation in an unclean area, often the mouth. The eruption may become papular, but angina is usually absent.

2. *Papular Rashes.* The rash may be originally papular or may become so after an initial erythematous stage.

3. *Urticarial Rashes.* The association of urticaria with toxic conditions is of course well known; there is evidence that toxins which are bacterial in origin may cause a rash of this kind.

4. *The Hemorrhagic Group.* The lesions vary from minute petechiæ to extensive purpuric stains. They may be confined to the skin or associated with hemorrhages in the retina and elsewhere. In some of the cases the involvement has been symmetrical (both arms and both legs); in others the whole body has been covered and the picture that of hemorrhagic variola. In a case reported by Litten, attention was called to the rapid evolution of the lesions, increase in size, and coalescence occurring under the artist's eyes with such rapidity that it was difficult for him to get a good picture. I have already mentioned that rapid evolution was a feature of my case. In some cases a pustule has formed at the centre of the purpuric spot.

Spotted hemorrhages in septicemia are of serious prognostic significance; they are more frequent in the bad cases, and according to Lenhartz have been present in about 50 per cent. of the fatal ones. Attention has already been called to the fact that Bacillus mucosus capsulatus seems to be rather prone to produce a septicemia of the hemorrhagic type.

5. *Vesicles, Pustules, and Pemphigoid Eruptions.* These are not frequent, though one may see them in association with the commoner rashes (erythema, roseola, urticaria, etc.), or one may see an evolution from one of the simpler exanthems, through a vesicular

stage to a pustular or pemphigoid eruption. Gussenbauer reported an urticaria following a septic gangrene of the lower leg, in which many of the lesions were transformed into vesicles containing bloody fluid. Bamberger was one of the first to report a case of pyemic pemphigus; since his publication the condition has been rarely seen, and only in cases of severe septicemia. When the eruption is vesicular the vesicles may arise from urticarial or ecchymotic spots, and may develop into pustules followed by ulceration. In a remarkable case reported by Unna the eruption was pock-like.

6. *Herpes.* Herpes labialis does not appear to have been a particularly frequent feature of pyogenic septicemia, to judge from the reported cases. This is rather surprising when one considers its frequency in diseases like typhoid fever, the exclusion of which from septicemia is purely a matter of nomenclature. Herpes labialis does, of course, occur in pyogenic septicemia; the statement that it is more common in toxic than septic conditions is probably in part due to the fact that when this has been the only cutaneous lesion present the case has not been considered interesting enough to report, and therefore has not gotten into the literature.

CONCLUSIONS DERIVED FROM FURTHER EXPERIENCE IN THE SURGICAL TREATMENT OF BRACHIAL BIRTH PALSY (ERB'S TYPE).

By Alfred S. Taylor, M.D.,

CONSULTING SURGEON, HOSPITAL FOR RUPTURED AND CRIPPLED, TARRYTOWN HOSPITAL, WHITE PLAINS HOSPITAL; VISITING SURGEON, FORDHAM HOSPITAL; ASSOCIATE SURGEON, NEUROLOGICAL INSTITUTE; ASSISTANT SURGEON, BABIES' HOSPITAL; SPECIAL LECTURER ON SURGERY OF THE PERIPHERAL NERVES AT CORNELL UNIVERSITY MEDICAL SCHOOL, NEW YORK.

In 1905 Clark, Taylor, and Prout published[1] "A Study on Brachial Birth Palsy." The clinical portion of the study was based upon 7 operative cases. Since that time 36 additional cases have been operated upon, making 43 altogether. These have varied in age from four weeks to nineteen years.

Owing to the long lapse of time between the operation and the appearance of the end results in these as in many other cases of nerve suture (often two to three years) it has not been possible to follow many of the series as systematically and persistently as would be desirable for satisfactory case reports. Nevertheless the frequent operative contact with these lesions, the prolonged struggle involved in the after-treatment, and the constant con-

[1] Amer. Jour. Med. Sci., October, 1905.

sideration of the problems involved have led to certain convictions which are worth presenting for discussion to those interested in this subject.

As to etiology there is no question that the chief factor lies in the forcible separation of the head and neck from the corresponding shoulder, whether it occurs through too forcible instrumental traction when the shoulders are impeded, or whether the head and neck are used to pry out the shoulder from under the pubis, or whether, in a breech, too great traction is put upon the shoulders for the delivery of the after-coming head.

A few mild cases of the palsy have occurred where spontaneous delivery has relieved both instruments and accoucheur of any participation as active etiologic factors. Such cases should render us loath to put the responsibility in any given instance upon the accoucheur, yet nevertheless he, by a proper grasp of the mechanics of the thing, can nearly always avoid doing, and can often prevent Nature from doing, what would tend to cause this very serious lesion. If any obstetrician will make a simple apparatus like Fig. 1 he can readily work out the essence of the etiology.

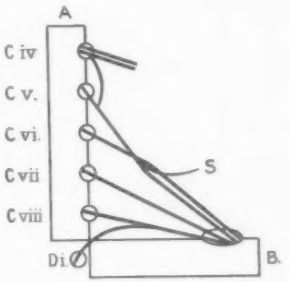


FIG. 1.—Schematic representation of brachial plexus. *A*, spinal column; *B*, shoulder; *S*, suprascapular nerve; *C*iv to *D*i, roots of plexus. If *A* and *B* are pulled away from each other *C*iv and *C*vi would first be put on the stretch. After they had yielded *C*vii would be involved, and so on down the line. *S*, the suprascapular nerve, would always be damaged first and most. If *A* and *B* are approximated the roots are relaxed, or if they have been torn the ends would be approximated. This should be the aim of treatment in all fresh cases.

In the original study only extraspinal lesions were considered. These, in brief, consist of rupture of the deep cervical fascia lying in front of the roots of the plexus, of rupture of the perineural sheaths, and finally of the nerves themselves, together with the vessels of all three structures. The resulting mass of torn fibrous tissue, nerves, vessels, and blood-clot organizes into a firm cicatrix which does not permit the passage of nerve impulses. The roots usually rupture in order from above downward, and the lesion involves one or more or all of them according to the degree of force used in causing the injury.

In addition to these extraspinal injuries there have undoubtedly been intraspinal lesions much more frequently than had been supposed. Where the roots are torn from the cord, hemorrhage occurs and the organization of the clot later causes cicatricial

deformity of the corresponding portion of the cord. This type of injury has been demonstrated by Dr. George Boyer, of Toronto,[2] in the case of a woman, aged forty years, who had borne such an injury through life.

It is not possible to state, with proof, that both extraspinal and intraspinal lesions occur in different roots of the same plexus, but the findings in certain of the cases operated upon most strongly indicate that such is the fact. For instance, in one of the late cases of the series there was a typical palsy of the upper arm type, fairly good motion about the elbow-joint, and complete flaccid paralysis of the hand, with marked atrophy of its intrinsic muscles. On dissection there was the usual cicatrix in the fifth and sixth roots extraspinally. The condition of the hand meant a serious lesion of the eighth cervical and first dorsal roots, but these, extraspinally, appeared undamaged, and on splitting their sheaths showed normal appearing fasciculi. There must therefore have been intraspinal damage to the two lowest roots of this plexus.

As previously stated the damage nearly always extends from above downward in the order of the roots, and involves from one to all the roots according to the degree of force used in causing the injury.

The damaged area in any given root may lie at any point between the spinal cord and the place where the final nerve trunks are given off from cords of the plexus. The lesion may consist of a circumscribed cicatrix involving a part or the whole of the root at any part of its course, or of several cicatrices scattered along its course, or of one large cicatrix involving practically the whole root. One cicatrix may involve two neighboring roots, this being commonly the case with the fifth and sixth roots, or may involve all the roots of the plexus when it has suffered complete rupture.

One or more of the roots may be completely torn across, the ends widely separated and grown fast to neighboring structures by scar tissue.

In all these cases the layer of deep cervical fascia lying just in front of the nerve roots is torn and always becomes adherent to the underlying nerves in the healing process. In certain rare cases the deep fascia alone is injured, adheres to the underlying nerves, and by cicatricial compression interferes with their functional activity.

With the exception of the intraspinal lesions, which could not be demonstrated anatomically, my series of 43 operative cases has illustrated each of the types above mentioned, and if one's operative experience were sufficiently extensive, he might expect to see an example of every type mathematically possible.

When the lesion is intraspinal, or when the cicatrix involves the

[2] Pro. Royal Soc. Med., 1911 (Neurological Section), v, 31 to 56.

root well into the intervertebral canal, operation as at present performed offers little prospect of improvement. Whether some modification of procedure will benefit these cases remains to be seen. Implantation into a neighboring root has been tried in a recent case, but there has not been sufficient time for results to appear.

Following permanent interference with nerve function, certain secondary pathologic changes develop, the importance of which was not appreciated fully until after a considerable experience with the postoperative treatment of these cases, and which have a most decided bearing upon determining at what age surgical interference should be insisted upon. The bones of the extremity do not develop normally. The clavicle is small, the scapula is small, the coracoid process is often drawn downward and forward, forming a beak which interferes with free mobility of the joint, and the glenoid process maintains its infantile form. The upper end of the humerus remains infantile, and this, together with a similar condition in the glenoid process, renders easy the posterior dislocation seen in a certain proportion of these cases, which will be referred to later in dealing with symptomatology.

Constant maintenance of the elbow- and wrist-joints in the faulty positions characteristic of these cases causes the plastic bones of infancy to develop in somewhat abnormal shapes in their joint ends. Moreover, contractures in the paralyzed muscles and in the ligaments about the joints serve still further to fix and accentuate the deformities of the extremity as time goes on.

Thus the characteristic deformity seen just after birth is a purely functional one, and is due to the muscular imbalance resulting from the paralysis of certain groups of muscles. When, however, the paralysis persists through the early months or years of rapid growth the deformity, at first functional, becomes fixed mechanically by the organic secondary pathologic changes above enumerated. If late surgical intervention succeeds in obtaining good nerve regeneration, and this is usually the case, there still remain as serious obstacles to free motion these organic structural changes which enormously increase the period of postoperative treatment and prevent the attainment of a completely satisfactory ultimate result.

From this description of the incidence and sequence of pathologic events in these cases it is self-evident that in the great majority of instances there will be permanent interference with the transmission of nerve impulses in greater or less degree, and this degree will depend upon the number of roots torn and upon the distribution and extent of the resulting cicatrices. Inasmuch as the roots are almost always injured one after the other in order from above downward the muscles paralyzed naturally fall into the groups related to the primary roots of the plexus for innervation.

The great majority of the cases are of the "upper arm type," in which the injury involves the fifth and sixth roots. These two roots join soon after their exit from the intervertebral foramina, and this junction, which is often 1 cm. or more long, again divides to form trunks which enter into the plexus. From the outer edge of this junction is given off the suprascapular nerve. Injury to these roots is usually at their junction, or just above it, or at and just below it. In a smaller proportion of cases they are damaged at or within the intervertebral foramina, and rarely torn from the cord itself.

A study of the schematic plexus, Fig. 2 (Kocher), will indicate better than much description the muscle groups related to the different nerve roots and what must be the result of different root injuries.

While the schematic plexus is not accurately drawn a study of it will show how one may get some approximate idea of the situation of the lesion from the grouping of the symptoms. The branches to the deep muscles of the neck as well as those forming the posterior thoracic nerve come from the roots soon after their exit from the intervertebral foramina, so that if the rhomboids, the scaleni, and especially the serratus magnus are paralyzed one may deduce that the lesion extends up to if not into those foramina.

The more common lesion occurs distal to the origin of these branches, so that the winged scapula significant of serratus paralysis is not so frequently seen.

The usual picture in the newborn child is that of a complete flaccid paralysis of the extremity which lies close along the side with the elbow and wrist straight and the fingers somewhat flexed. There is marked inward rotation of the entire extremity, with pronation of the hand. This total paralysis results from the fact that those nerves which have not been torn and permanently injured have been overstretched and temporarily paralyzed.

In the not rare cases where the entire plexus is ruptured this clinical picture is permanent. In the less severe cases the lower roots begin to functionate, so that after days or weeks, as the case may be, motion begins to appear first in the fingers, then in the hand, wrist, forearm, etc., up to the level of the permanent lesion. In still slighter cases these motions in the distal portions of the extremity may be present from the start.

As time goes on the permanently paralyzed muscles undergo contracture and cause the typical deformity seen in Fig. 3; they also atrophy. This atrophy is not so easily made out in the young infant because of the thick layer of subcutaneous fat which keeps the form of the extremity filled out.

In certain of these cases there develops after a time a posterior luxation or subluxation of the shoulder-joint. This results from a combination of factors. The complete paralysis of the spinati

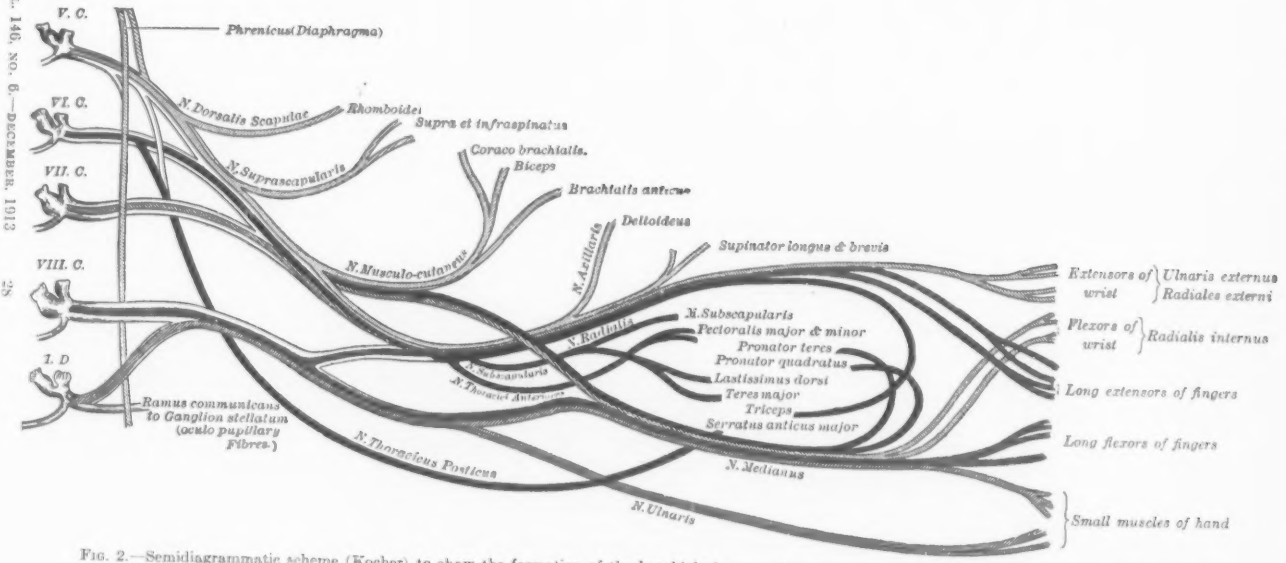


FIG. 2.—Semidiagrammatic scheme (Kocher) to show the formation of the brachial plexus and the nerve supply to the muscles of the upper extremity.

and deltoid leaves the posterior and external aspects of the joint without the usual muscular support. The persistent infantile shape of the glenoid fossa and the end of the humerus favor easy dislocation. The pectoralis major, being usually only partially paralyzed, strongly rotates the humerus inward and exerts some pressure backward upon it. When the subscapularis, teres major, and latissimus dorsi escape partially or wholly from the paralysis they add much to the inward rotation and posterior displacement of the upper end of the humerus.

FIG. 3.—Typical deformity in a late case. Note the small size of the entire extremity, the marked inward rotation and pronation, the flexion at the elbow, the marked flexion, and ulnar adduction at the wrist.

This posterior displacement occurs in greater or less degree in every case, and can be made out readily by careful comparison with the opposite normal shoulder. The extreme degree of this displacement results in complete posterior luxation. When the biceps and coracobrachialis suffer from contracture there is an added upward thrust to the head of the humerus which brings it well up under the acromion process.

In the literature these complete posterior dislocations not infrequently appear under the title of "Congenital Posterior Dislocation of the Shoulder." One Boston, one Philadelphia, and one

New York case are on record in which operative procedures upon the shoulder-joint itself were done, with the idea of reducing the dislocation. In one of the three where reduction was impossible the head of the humerus was resected.

The histories, the pictures of the characteristic attitudes of the extremities, and the results in these cases leave practically no doubt that they were really examples of brachial plexus injury at the time of birth. These cases accent the necessity of the surgeon's associating a neurologist with himself in the care of these obscure congenital deformities about the shoulder-joint.

From infants it is practically impossible to derive any satisfactory information as to sensory disturbances in these arms, and by the time they are old enough to examine satisfactorily, sensory disturbances have disappeared except possibly in the cases of severe injury where some hypesthesia or anesthesia may persist.

There is regularly interference with the growth of the extremity.

One symptom which was worked out by Clark and presented in the original study is not sufficiently comprehended and appreciated. Careful palpation of the region of the fifth, sixth, and seventh transverse processes invariably makes out a characteristic induration which varies with the severity of the lesion, and which is always sensitive to pressure. The examiner should approach the sitting child from the rear and palpate both sides of the neck at the same time to compare the normal with the damaged side.

This induration seems to be less marked in those cases where the roots have apparently been pulled from the cord.

The meat of this problem lies in the question of prognosis in these cases when they are not treated surgically. Upon a proper conception of the prognosis must depend the system of treatment which will lead to the best ultimate results.

Most text-books give an optimistic prognosis. For instance a well-known pediatric text-book says: "The great majority of cases recover spontaneously in two or three months, improvement being observed within a few weeks. Spontaneous recovery is not to be looked for unless it occurs within the first three months. Not infrequently some degree of paralysis persists until the third or fourth year, and in some of the muscles, especially the deltoid, it may even be permanent."

A well-known text-book on neurology says: "Many of these cases go on to spontaneous recovery within six months after birth. Others remain longer and do not recover within the first year. The condition may remain for three or four years and pass away only when the child is old enough to be taught systematic gymnastic exercises."

These quotations are evidently optimistic. As a matter of fact in all these unfortunates (except where the entire plexus has been

ruptured) spontaneous improvement appears after an interval of three to twelve weeks after birth and continues slowly until the child is about two years old. After this time improvement ceases and the pathologic sequels previously mentioned cause increasing deformity and interference with function.

This long period of time over which spontaneous improvement occurs is to my mind the chief cause of the firmly fixed but entirely erroneous belief with regard to the prognosis in these cases. The mothers take their infants to the clinics, are told that the outlook in most instances is good, and are invited to come regularly for manipulation and electricity. After a time improvement sets in and progresses steadily. After a further interval, pressed by other demands upon her time and relieved of her mental anxiety by the prognosis of ultimate spontaneous recovery, the mother ceases to attend the clinic. The physician, looking over his records, and remembering the continuous improvement over a period of time, attributes the further non-attendance to spontaneous recovery. If, however, he would visit any of the orthopedic dispensaries he would find many of these children applying for treatment at a time when the mothers had given up hope of the recovery which had been held out to them in the infancy of the victims.

Recently a child, one year old, was brought in by its mother. It had a marked paralysis still persisting with absolute flaccid paralysis of the wrist and hand. Yet when this child was only three months old he was taken to one of our well-known neurologists, who examined him and then told the mother to rub the arm, put it through passive motions for the joints, and it would come around all right. The hopelessly crippled extremity at the end of a year led the mother to consult an orthopedic surgeon, who referred him for immediate operation. At operation C VI, VII, VIII, and D I were completely torn across and regeneration could never have occurred.

This kind of history is repeated again and again in our operative cases, and this attitude on the part of the profession at large does more than anything else to prevent these unfortunate cripples from obtaining the best treatment at the best time.

Let me say, with as much emphasis as possible, that my personal experience convinces me that the prognosis in these brachial injuries is exceedingly bad; that complete spontaneous recovery is rare, occurs only in mild cases, is complete usually by the end of three months, and almost never later than six months. In the vast majority of cases there will be a permanent defect.

Until the true prognosis permeates the general profession the surgical repair of these lesions will never have its best opportunity, and anyone who follows these cases for a sufficient length of time will become convinced that surgery alone holds out the best hope to the great majority of them.

Having arrived thus far the one great thing is to choose the best time for operative interference.

It is generally admitted that nerve generation and regeneration are most active in young infants.

Here as elsewhere in the peripheral nervous system the sooner a divided nerve is sutured end to end the better is the prospect of a satisfactory result.

Within a few weeks or months of birth the secondary pathologic changes previously enumerated begin to develop, causing a mechanical fixation of the extremity in its deformed attitude. The longer this fixation has persisted the more tedious will be the after-treatment.

From the above premises the only logical deduction would be immediate operation. However there are some reasons for temporary delay. It is unwise to subject a newborn babe to anesthesia until it has had a short time to adjust itself to its new surroundings and to show how competent its digestive apparatus is to be.

The damaged tissues should have time to regain their normal resistance to infection. Instead therefore of demanding immediate operation, which would be best from the standpoint of nerve repair, we must demand operation at the earliest feasible moment considering the general condition and the local resistance of the individual child. Under these circumstances the choice of time for operative interference may vary from two weeks to three months. Seldom will it need to be postponed beyond three months.

It will be noted that in laying down the indications for operation nothing has been said with reference to spontaneous regeneration and recovery. The plan of waiting until spontaneous improvement has ceased is the greatest imaginable stumbling block in the way of obtaining the best results in this whole class of patients, for the reasons mentioned under "secondary pathologic changes." In all cases where a really complete spontaneous recovery will occur the primary paralysis will be of only moderate degree and obvious improvement will begin within the first couple of weeks. In every case where there is considerable paralysis and where no improvement begins within the first few weeks there is certain to be some degree of permanent injury to the roots.

In every case where this permanent injury is indicated, and in every case where it is even debatable whether permanent injury has occurred, operation at the earliest feasible moment, as above indicated, should be performed.

In these operations the chief risk lies in the anesthetic, because the wound goes only through skin and fatty tissues; with experience the loss of blood may be limited to one or two teaspoonfuls; the shock is negligible, and the time consumed varies with the complexity of the lesion found.

In the debatable cases the procedure might better be called an

exploration rather than an operation. If no lesion demanding nerve resection and suture be found the wound is promptly closed and the whole thing is over in fifteen minutes, with no chance of harm to the child. It amounts to nothing more than the making and closing a skin incision, which permits inspection and palpation of the roots, with precise knowledge upon which to found the after-treatment for the individual case.

If on the other hand a definite lesion is found it is resected and followed by end-to-end suture, and this is done at the time which is obviously the best for the child's future.

The newborn victim of this injury is caused to suffer much pain and detriment because of the advice commonly given to the parents —namely, "to start at once with massage, passive motion, and (possibly) electricity."

One should remember that the original injury starts a traumatic neuritis, which is aggravated by massage and passive motion, especially about the shoulder region. This added irritation causes more scar tissue to interfere with nerve regeneration. Moreover, the victim is caused an unnecessary amount of pain.

In all these cases the best primary treatment would be to keep the injured extremity at rest for at least two weeks. This might best be done with an ordinary triangular sling so arranged as to derive all its support from the sound shoulder and to cause marked elevation of the shoulder on the damaged side. This method obviously removes all strain from the plexus, and, in case any of the roots are torn, approximates the ends and gives the best opportunity for spontaneous repair.

At the end of two weeks the sling may be removed daily and gentle massage given, always with care not to pull the shoulder away from the head and neck, as this would again stretch the damaged nerves.

At the end of three weeks decision should be made for or against operative exploration, and, if operation is chosen, it should be done as soon as the particular child can stand it.

Some variations from the operative technique published in the original study may be worth mentioning.

In extensive lesions the incision there described, running from the lower third of the sternomastoid to the outer third of the clavicle, gives the best working exposure. For less extensive cases, and in young children where the tissues are elastic, an incision from the insertion of the sternomastoid running outward and slightly upward, following the natural wrinkles in the skin at the base of the neck, will give a satisfactory exposure, and heals with a scar that will never spread. The first incision heals by primary union satisfactorily, but later always spreads into a broad, flat, white scar, which is objectionable in females.

Where there will be tension on the nerve suture, silk is the preferred material. In young infants in whom the working space and the nerves are small, and where there is less likelihood of much tension on the sutures, a purse-string suture of fine chromic catgut answers.

In infants a few weeks old the dissection is comparatively easy because the scar tissues have not become firm and the nerves are readily identified. Apposition is also easier.

The older the child the firmer the scar tissues become, and the more difficult is the dissection. In some of the older cases, where some of the roots have been torn completely across, the ends displaced and later bound by firm adhesions to neighboring structures, a field for dissection is provided in which the greatest patience, endurance, and skill in anatomical orientation is requisite to ravel out the mysteries contained in the blanket of scar tissue.

In those cases where a root or roots have been torn from the cord they must be anastomosed into a neighboring root, with the hope of getting a distribution of power. This procedure has been done within the last few weeks in a child and in an adult after an avulsion of the C VIII and D I from the cord.

When the nerve sutures are placed, and if there is more than one they must all be placed before any of them are tied, the head, neck, and shoulder are approximated. This position must be maintained without a moment's relaxation. The sutures are tied from below upward, the skin wound is closed with silk, a sterile dressing applied, and appropriate fixation accomplished. This fixation apparatus must hold the head and shoulder in close approximation without a moment's cessation for from three to twelve weeks from the time of operation, according to the individual case.

In the early cases a plaster splint, fashioned before operation, was used, but it proved not only to be heavy, clumsy, and uncomfortable, but, worst of all, after ten days became so limp as no longer to maintain the necessary position.

A steel brace was then devised (Fig. 4), and this has served its purpose without undue discomfort to the patient. In the case of young children, when it is properly applied, it permits free handling for bathing and dressing, and is not much in the way of the clothing.

The brace is made of flat steel rod appropriately bent and supplied with supports for the forearm and shoulder. A muslin cap is fitted to the child's head, the edges of which are turned up over the head part of the brace (Fig. 5). This prevents the head from protruding too far through the brace. An adhesive plaster strap is started from the top of this cap, passes down the cheek of the well side, and across under the chin to the shoulder pad of the brace. The shoulder pad, which overlies the scapula of the damaged extremity, is fastened by a broad adhesive strap which passes from

the pad obliquely downward over the child's back (Fig. 6). The forearm and arm are bandaged to the brace.

FIG. 4.—Steel brace, showing grooved channel for the forearm and hand, a large pad to hold the shoulder forward, and the upper curved band to encircle three-quarters of the head. The whole thing is padded and covered with leather.

FIG. 5.—The brace applied, elevates the whole extremity so as to approximate the shoulder to the neck. The upper part, with a muslin cap stitched to it, holds the head down and to the damaged side. The chin strap prevents the child from getting its head out from under the brace. The shoulder pad, fitting over the scapula, holds the shoulder from being displaced backward. The net result is to hold the child fast with the head and neck and shoulder closely approximated so as to relieve the strain on the nerve sutures. This position is the one that should be adopted in every fresh case so as to approximate the damaged nerve ends and give the best chance for spontaneous healing.

This brace must be carefully fitted and adjusted before operation, or pressure sores are apt to develop and complicate the postoperative treatment.

Many parents and even practitioners express the fear that wryneck will follow the prolonged fixation of the neck. In my whole series of cases that complication has not appeared a single time.

The after-treatment is an exceedingly important part of the care of these children. It starts with the removal of the brace, and at first should consist of massage and passive motion applied to the fingers, hand, wrist, forearm, elbow, and muscles of the arm. For an interval of four to six months after the operation, manipulation about the base of the neck and shoulder should be used with great care to avoid putting strain upon the sutured nerve roots. For the same reason such manipulation as is given to the remainder of the extremity should always be conducted in a way not to pull the shoulder away from the neck or downward.

FIG. 6.—Showing the posterior view of the brace, with a broad band of adhesive plaster running from the shoulder pad obliquely down across the back. The cap, which was just pinned on for the picture, has become distorted in the child's wriggling.

Electricity, while not essential, is of some value, and often helps to keep the parents at systematic treatment.

After sufficient time has elapsed for absolutely firm union to have occurred in the sutured roots, manipulations about the shoulder should be more vigorous. The greatest difficulty to overcome lies in the contractured pectoralis major and the shortened anterior capsule of the joint. It may be necessary to stretch them under an anesthetic or to lengthen the pectoralis tendon. These troubles ensue only in the cases which have been too long neglected before operation.

As the evidences of nerve regeneration appear the child must be educated to use the muscles, heretofore functionless, by means

of gymnastic exercises, games, workshop methods, etc. These methods must be followed systematically for several years to get the best results after operation.

The first question asked always is, What are your results?

To allay any suspicion of overenthusiasm or radicalism I may state frankly that I never have seen a perfect arm result from operation nor do I ever expect to. There is always failure to reach perfect function to a greater or less degree.

On the other hand in the great majority of cases there will result a degree of improvement which can be attained by no other method than the surgical repair of the damaged nerve roots. Several of the series operated upon had been given systematic physical therapeutics over a period of two years, with so little result that the parents turned to operation as a last resort. The results were a great improvement over anything obtained by the previous efforts.

If the operative technique and after-treatment are properly carried out the results will always be worth the trouble.

Instead of publishing a long list of case histories I shall illustrate the value of operation by detailing one case, with serial photographs, in which the entire result must be credited to the surgical interference because there had been complete rupture of the plexus, and there had been absolutely no spontaneous improvement during the year of life.

Ruth F. (Case 9 of my series), aged one year.

History. She was the second child of the family, was large, and was delivered with instruments after a difficult labor. Soon after birth it was noticed that the left upper extremity was lifeless. There has never been any improvement in it in spite of intermittent treatment received in various clinics. Except for the arm she has been perfectly well.

Examination. She is a large, well-nourished child, normal except for the left upper extremity, which hangs lifeless by her side (Fig. 7). There is some power in the serratus magnus, contraction of which, with some contortion of the trunk, throws the extremity slightly forward. The soft tissues are flabby and the extremity is cold. The muscles show reaction of degeneration. A large indurated mass can be felt on the left side of the neck at the site of the brachial plexus.

Operation. June 8, 1905. Ether anesthesia. The plexus was exposed by the usual dissection. The deep fascia was thick and adherent to the front of the whole plexus, which was itself one large mass of cicatricial tissue, with the nerve roots running into it above and the nerve trunks coming off from it beneath the clavicle. The roots were divided above the cicatricial mass nearly at the foramina. The plexus was removed *en masse* by dividing the nerve trunks as they emerged from its distal end beneath the

clavicle. In attempting end-to-end suture the nerve ends could be approximated to within only 2 cm. of each other, so loops of chromic gut (No. 1, 40 day) were passed through the roots and distal trunks and surrounded *en masse* with cargile membrane. The suprascapular nerve was carefully included in the suture. The wound was closed without drainage and the head and neck bound in close approximation. This fixation was maintained six weeks. (At the present time I should hold the position for at least twelve weeks, which I could easily do with the steel brace.) The reaction was good. Primary union resulted.

FIG. 7.—Rupture of the entire plexus on the left side. Note the completely paralyzed, flaccid hang of the left extremity while she is playing with something in the right hand.

Postoperative History. This child was brought for examination only at irregular and infrequent intervals. At the end of three months the muscles were more flabby than ever, the shoulder was a flail-joint, and there was no sign of returning power.

December 21, 1905, six months after operation, the mother first noticed that the terminal joints of the thumb and index, middle, and ring fingers were swollen, glossy, red, and ulcerated on the tips. They were not sensitive and were not infected. They remained in this condition for about six weeks, and then gradually the fingers improved, until, on May 21, 1906, they were almost normal again.

While this trophic disturbance was present in the digits, there

was, on December 21, 1905, distinct but slight activity in the pectoralis major, triceps, and serratus muscles.

May 21, 1906 (one year less eighteen days), the movement in the above muscles was stronger. There also appeared some power

FIG. 8.—Eleven and one-half months after operation.

FIG. 9.—Same as Fig. 8. Lying on her back she is able to raise the arm perpendicularly.

in the deltoid, both for anterior elevation of the arm and slightly for abduction (Fig. 8). There was also slight power of flexion at the wrist. When she was lying supine she could elevate the entire extremity to a perpendicular with the floor without much effort

(Fig. 9). At this time there was distinct contracture of the flexor muscles of the fingers. The mother had neglected the massage. The shoulder had lost its flail-like character and the muscles of the whole extremity were firmer.

October 27, 1907 (two years and four months). The flexion contracture of the fingers had entirely disappeared. She had been using the extremity freely for the preceding six months,

FIG. 10.—Sixteen and a half months after operation. Note the improved size and position of the hand and arm.

FIG. 11.—Same as Fig. 10. Voluntary flexion at the elbow with some supination of the forearm.

handling playthings, feeding herself with it, etc. All of the muscles showed some return of voluntary power, although the flexors of the fingers and extensors of the radial carpus were quite feeble. The extremity had grown very well.

February 4, 1908 (two years and eight months). Marked improvement in all the movements of the extremity. She can put the hand to the mouth easily. There is fairly strong flexion and extension of all the digits.

February 1, 1910 (four years eight months). Marked increase in power of muscles. Can do things with the separate fingers.

February 7, 1911 (five years eight months). Marked increase in power and definite control of the muscles. The whole extremity is smaller than the right one.

SUMMARY. The essential etiologic factor consists in the forcible separation of the head and neck from the shoulder on the side of the lesion.

FIG. 12.—Same as Fig. 10. Anterior elevation of the extremity so that wrist is at the level of the hair line. The hand is still useless.

FIG. 13.—Same as Fig. 10. Abduction at the shoulder showing activity of the deltoid.

Pathology. The deep cervical fascia, the nerve sheaths, the nerves, and small accompanying vessels are torn. After a time the resulting blood-clot and torn structures form a dense cicatrix which prevents nerve regeneration. As a rule the injury involves the roots in order from above downward, and may vary in extent from a slight injury of the upper root to a complete rupture of the entire plexus. In some cases roots are torn from the cord itself. Secondary pathologic changes occur in the muscles, ligaments, and joint-ends of the bones.

Symptoms. The paralyzed muscles fall into groups according to the roots injured. The characteristic attitude is one of marked inward rotation of the whole extremity, which is accented by the pronation of the forearm and hand. There is always some posterior displacement of the upper end of the humerus as compared with the normal side, and in a small proportion of cases there is complete posterior dislocation of the shoulder. Sensory disturbances are slight and usually soon disappear. Interference with growth

FIG. 14.—Three years after operation. Showing growth of arm and hand.

FIG. 15.—Same as Fig. 14. Showing sufficient strength to support a large heavy doll upon the forearm and hand.

is always present and is most marked about the shoulder girdle. Deformity usually increases with age. A cicatrix can easily be felt in the region of the damaged nerves, and is usually tender even after years.

Prognosis. Prognosis is bad. There is nearly always some degree of deformity and paralysis which persists.

Operation. Operation gives the best prospect for a useful arm. The best time for operation is as early as the general condition of the individual patient will permit (three to twelve weeks). In

the few cases in which complete spontaneous recovery will occur the paralysis is usually not extensive, improvement starts early and continues rapidly, and operation is evidently contraindicated. In debatable cases operation really amounts to early exploration, with repair of such damage as may be found. There is exceedingly little danger to the operation, which amounts only to an incision through the skin and fat at the base of the neck.

FIG. 16.—Same as Fig. 14. A light rubber doll grasped in the hand (that is, lifted from a chair by the left hand) and held forward of the body with the elbow flexed. This child had a complete rupture of the plexus and complete flaccid paralysis of the whole extremity.

Up to the time of operation the extremity should be held up in a sling to take its weight off the damaged nerves and paralyzed muscles.

In the cases where roots have been torn from the cord they must be laterally implanted into the neighboring roots, or if the neighboring roots have been damaged enough to require resection all of the distal nerve trunks may be sutured in a bunch to the proximal roots still attached to the cord.

After operation the head and shoulder must be held in approximation for weeks by a steel brace fitted before operation.

After-treatment must be systematic and persistent.

Results will never be perfect, but operation will give improvement much greater than that obtainable by any other method.

FURTHER EXPERIENCES WITH STRETCHING OF THE PYLORUS.

By Max Einhorn, M.D.,

PROFESSOR OF MEDICINE AT THE NEW YORK POSTGRADUATE MEDICAL SCHOOL, NEW YORK.

In four[1] previous papers I have shown that the pylorus can be stretched by way of the mouth. I have described the necessary technique and reported a number of cases treated by this method.

In the present article I purpose reviewing briefly the old cases in whom the pylorus had been stretched, with regard to their results, and then to report my new experiences along this line. Altogether, there were 12 cases in grown people and 3 in infants, in whom the pylorus was widened. Of the infants, 2 were cured and remained well, 1 died about ten days afterward, that is, the stretching did not accomplish the desired benefit.

Of the 12 grown patients 9 remained well, 1 had a perforation of the diagnosed duodenal ulcer (Miss J. C. C.) two years after treatment and was operated successfully, 2 died: 1 about a year later from the results of a gastric hemorrhage (H. T.), the other (Dr. F. L. C.) from a return of the stricture of the pylorus. He was advised to be operated, but refused and succumbed some months later.

The new cases treated during 1912 and up to July, 1913, have been embodied in the subjoined table, and but three of them are here described.

By referring to the table, it will be found that the pylorus was stretched in 21 patients.[2] The number of stretchings amounted to 100. In 3 patients [E. C. A. (5), W. J. McC. (13), and Rev. M. J. D. (6)] the pylorus had to be stretched over the thread by means of the pyloric dilating catheter, for the pylorus was too narrow to admit the passage of the usual pyloric dilator. In patient Rev. M. J. D. the latter instrument could then be employed. In two patients (Rev. W. H. W. (2) and A. D. S. (7) the double balloon pyloric dilator was used off and on, in order to stretch the pylorus *in situ* for a somewhat longer time (one to two minutes). This mode of stretching is more effectual, but at the same time more difficult to accomplish. The patient is compelled to swallow a somewhat larger instrument and the physician has to know the exact amount of air which he may instill into the dilating balloon.

[1] Max Einhorn, Dilatation of the Stomach and Chronic Benign Ischochymia, Illinois, Med. Jour., June, 1910; On Pylorospasm, Med. Rec., January 21, 1911. Stretching of the Pylorus in Benign Stenosis, Med. Rec., June 10, 1911; Widening the Pylorus without Operation, New York Med. Jour., May 11, 1912.

[2] Nineteen entirely new, and three (Cases 1, 3, and 8) which had been described before, but in which the stretching of the pylorus was continued during 1912.

TABLE OF NEW CASES IN WHOM THE PYLORUS WAS STRETCHED.

No.	Name.	Diagnosis.	Gastric secretion.	Ischochymia or hypersecretion.	Date of stretching and size of pylorus.	Result.	Remarks.
1	Dr. L. C.	Dilatation of stomach; benign stenosis of pylorus	HCl + Acid = 75	Slight ischochymia and considerable hypersecretion present.	1911—Oct. 17, 21, 24, 31 (50 mm.); Nov. 13 (52 mm.), 24 (55); Dec. 22, 28. 1912—Jan. 9 (60 mm.); Feb. 19; March 3, 24 not passable; April 1, 3, 16; May 7.	Good; stomach regained almost normal motility up to March; then relapse.	Patient had first gained twenty-three pounds, but later grew worse.
2	Rev. W. H. W.	Ulcer of the stomach; pylorospasm.	HCl + Acid = 90	Slight hypersecretion present.	1911—Nov. 16, Dec. 3. 1912—Jan. 2, 16 (46 mm.); Feb. 15, (50 mm.); Mar. 6, April 18, May 23.	Good; pains and hypersecretion ceased.	
3	Mrs. B.	Gastric ulcer. Dilatation of stomach, with benign stenosis of pylorus; movable kidney.	HCl + Acid = 48	Slight ischochymia present.	1912—Jan. 5 (38 mm.), 10 (40 mm.), 18 (44 mm.); 30 (44 mm.); Feb. 21 (50 mm.).	Normal motility; gained fifteen pounds in 3 months.	
4	Miss F.	Gastric ulcer; dilatation of stomach; pylorospasm.	HCl + Acid = 75	Neither ischochymia nor hypersecretion present.	1912—Jan. 11 (60 mm.).	Felt better; gained some.	
5	E. C. A.	Benign far-advanced stricture of pylorus; cirrhosis of liver.	HCl + Acid = 80	Pronounced ischochymia present.	1912—Feb. 3, 17, 24; Mar. 2.	Good; good motility reëstablished; gained twenty pounds.	The stretching was done over the thread with the dilating catheter.
6	Rev. M. J. D.	Ulcer of the stomach; benign stenosis of the pylorus.	HCl + Acid = 100	Continuous hypersecretion present.	1912—Feb. 6, 23 (52 mm.), 28 (50 mm.); Mar. 5 (54 mm.), 12 (50 mm.), 20 (52 mm.), April 16 (55 mm.); May 7 (55 mm.) 28 (52 mm.); Oct. 9. (56 mm.).	Good; no pain; stomach empty when fasting.	
7	A. D. S.	Ulcer and dilatation of the stomach, with pronounced pylorospasm.	HCl + Acid = 116	Continuous hypersecretion and slight ischochymia present.	1912—Mar. 12, (50 mm.), 15 (56 mm.), 19 (66 mm.), 28 (56 mm.); April 7, 17 (65 mm.) May 12 (55 mm.), 19 (74 mm.), 26; June 3, 17 (60 mm.), 29 (60 mm.); Nov. 17 (56 mm.), 24 (60 mm.); Dec. 1 (70 mm.), 15 (70 mm.). 1913—Jan. 5, 12, 19, 26 (61 mm.); Feb. 15 (70 mm.).	Good; with regard to gastric motility.	Three months after the last stretching patient had a severe gastric hemorrhage. He was operated on three weeks later, beginning of July, and made a good recovery.
8	Mrs. H. H. W.	Anemia; gastric ulcer; beginning stenosis of pylorus.	HCl + Acid = 60	Neither ischochymia nor hypersecretion present.	1912—Feb. 23 (40 mm.); Mar. 4 (52 mm.); Sept. 26 (42 mm.), 28, 29 (45 mm.).	Good, free from pain, regained ten pounds in weight.	

9	E. S. M.	Bradycardia, dilatation of stomach and pylorospasm.	HCl + Acid = 96	Continuous hypersecretion present.	1912—April 10 (54 mm.).	Good.	
10	Eugene F.	Ulcer of stomach and pylorospasm.	HCl + Acid = 80	Continuous hypersecretion present.	1912—April 30 (49 mm.); May 12 (70 mm.).	Improved; pains less severe, but still present.	
11	E. C. M.	Gastric ulcer and beginning benign stenosis of pylorus.	HCl + Acid = 96	Continuous hypersecretion present.	1912—May 24 (38 mm.), 27 (46 mm.); June 14 (50 mm.), 27 (51 mm.); Sept. 10 (48 mm.); Oct. 1 (52 mm.), 18 (54 mm.)	Good with regard to pylorus; no pain; gained in flesh.	About five months after the last stretching had a gastric hemorrhage; operated by Dr. Blake; recovery.
12	H. P. R.	Ulcer of stomach; gastralgia tarda; pylorospasm.	HCl + Acid = 75	No.	1912—May 14 (50 mm.), 17 (54 mm.), 21 (46 mm); Sept. 13 (52 mm.)	Good, free from distress, gain in weight.	
13	W. J. McC.	Dilatation of stomach; stenosis pylori benigna, peristaltic restlessness; cirrhosis of liver	HCl + Acid = 90	Pronounced ischochymia present.	1912—May 28 (38 mm.).	Good temporarily in widening the pylorus and making duodenal feeding possible.	Patient was operated later by Dr. Willy Meyer; recovery.
14	Henry B.	Gastric ulcer; beginning stenosis of pylorus.	HCl + Acid = 70	No ischochymia.	1912—Sept. 24 (41 mm.), 28 (50 mm.); Dec. 15 (60 mm.), 19 (65 mm.), 23 (65 mm.).	Good, no pain, gain in flesh.	
15	Henry T.	Gastric ulcer near pylorus; pylorospasm.	HCl + Acid = 86	Continuous hypersecretion present at times.	1910—Oct. 29 (54 mm.).	Good.	
16	Marshall McK.	Dilatation of stomach and gastric ulcer.	HCl + Acid = 55	Continuous hypersecretion present at times.	1912—Nov. 26 (60 mm.), 29 (62 mm.).	Good.	
17	G. J. R.	Duodenal ulcer; gastralgia tarda.	HCl + Acid = 85	Continuous hypersepretion present at times	1913—Jan. 30 (58 mm.); Feb. 4 (58 mm.).	Good.	
18	Harold Du C.	Gastralgia	HCl + Acid = 65	No.	1911—May 18 (52 mm.).	Good.	
19	Frank D.	Ulcer of stomach near pylorus; pylorospasm.	HCl = 55 T.a.c. = 68	Ischochymia present in a small degree.	1913—May 6 (54 mm.),-13 (55 mm.).	Gastric motility good; gained in weight.	
20	Nicolas de C.	Enterit. chr. dilatation of stomach; pylorospasm.	HCl + Acid = 96	No.	1913—June 17 (60 mm.), 24 (65 mm.).	Good.	
21	Solomon M.	Dilatation of stomach and pylorospasm.	HCl + Acid = 100	Continuous hypersecretion present.	1913—April 1 (60 mm.), 8 (62 mm.); May 6 (60 mm.), 20 (62 mm.).	Good; no pains; gained in weight	

Among the patients treated by stretching, 8 had a real stenosis of the pylorus while 13 suffered from pylorospasm of varying severity.

In all my experiences with stretching of the pylorus, I have thus far encountered no mishap whatever. Two or three times the dilating balloon was somewhat tinged with blood, due to an ulcer situated in the pyloric vicinity, but even then there were no ill results.

The results were, as a whole, very good. The pains subsided and the ischochymia or hypersecretion, if present, decreased or disappeared.

Two of the patients reported in the table [E. C. M. (11) and A. D. S. (7)] improved with regard to their pylorus, but had, several months after the stretching, due to the presence of their ulcers, a return of gastric hemorrhages. Operation was performed in both by prominent surgeons, in one by Dr. Kammerer and in the other by Dr. Blake, with complete recovery.

As examples, we single out two cases of real pyloric stenosis and one of pylorospasm which we shall briefly describe:

Case I.—Cirrhosis of the liver and dilatation of the stomach and benign pyloric obstruction. W. J. McC. (13), aged about fifty-two years, began to be troubled with digestive symptoms about five years ago. Pains two to three hours after meals and occasionally vomiting were the chief complaints. After three years, which contained periods of suffering intermingled with intervals of euphoria, he went to Vichy and later to Nice, France, where he was treated by gastric lavage and a strict milk diet. He then lost considerably in weight, but, as a whole, felt better for a while. During the last six months, before consulting me, the patient was suffering all the time, frequently vomiting large quantities of gastric juice, with some food. He had meanwhile lost over sixty pounds in weight. Etiologically, it is important to state that the patient had smoked considerably and indulged freely in alcoholic beverages. The examination showed a markedly enlarged liver, extending to about one finger above the navel, and immensely dilated stomach; the latter reached to the symphysis, and showed continuously pronounced peristalic restlessness. The gastric contents revealed ischochymia and a high acidity: HCl + acidity = 100. The duodenal bucket, size No. 23 F., did not pass the pylorus. A smaller one, size No. 18, was given. When it was found that the latter had entered the duodenum, the pylorus was stretched by means of the pyloric dilating catheter. Although an operation was considered necessary, the patient was not in good shape to undergo it at this time, on account of the marked symptoms of inanition and the swollen liver.

After the stretching of the pylorus the duodenal pump was applied, and as soon as it passed into the duodenum, feeding through

the latter began. The patient then began to improve. He was free from pain and vomiting, and developed more strength and vitality almost daily.

The liver grew smaller, and on the eighth day of duodenal feeding was almost normal in size. On the tenth day, during the night, the tube slipped into the stomach and failed to reënter the pylorus. As the patient was much stronger now, the operation of gastro-enterostomy was advocated and performed by Dr. Willy Meyer. The patient made a complete recovery and remained well. Here, as is seen from the report, the stretching of the pylorus was of great benefit, allowing the patient to be built up and be in shape to stand the major operation.

Case II.—Ulcer of the stomach and benign stenosis of the pylorus. Rev. M. J. D. (Table, Case 6), aged about forty years, was suffering for the last three years from recurrent attacks of severe pains two to three hours after meals. There was occasional vomiting. Patient was treated by several physicians and advised to be operated. The examination showed a moderately dilated stomach, the greater curvature extending to about one finger below the navel, a high acidity: HCl + acidity = 100, with some minute ischochymia. The duodenal bucket, No. 23 F., failed to pass the pylorus, while No. 18 did. The thread showed ulceration of the lesser curvature of the stomach. Duodenal bucket, size No. 18 F., was again given, and the following morning the pyloric dilating catheter introduced over it and the pylorus stretched.

The duodenal pump was then given, duodenal feeding instituted for a period of two weeks, and then the pylorus was regularly stretched by the usual pyloric dilator. The patient made a splendid recovery, being able to eat ordinary food with impunity.

Case III.—Dilatation of the stomach and pyloric ulcer with pylorospasm. Frank D. (Table, Case 19), aged forty-three years, ropemaker. Habitual user of alcohol for many years. During the last nine years, he complained of distress and burning in the stomach, acid regurgitation, and occasional vomiting after alcoholic excesses. For the past two years his condition had become worse. He complained of pains in his stomach two hours after meals, lasting for two hours or more, frequently accompanied by vomiting of acid contents, which relieved the pain. During the past two years he lost twenty pounds in weight, and was obliged to live on a fluid diet, and was also unable to work. On April 4, 1913, the patient was admitted to the Postgraduate Hospital.

Examination on admission: poorly nourished man; weight eighty-four pounds. Chest negative. Blood and urine negative. Abdomen soft, no tumors; stomach gives splashing sound two fingers below umbilicus. Liver not enlarged.

Examination after test meal showed HCl, 55, and total acidity, 68; no blood. Duodenal bucket given on April 11, 1913, at night

and withdrawn in the morning, showed a yellow bile stain and a well-marked blood stain in the pyloric region.

April 14 to 28. Duodenal alimentation; weight, eighty-six and one-half pounds.

April 30. Duodenal bucket given and withdrawn in the morning, showed well-marked bile stain and no blood stain.

May 6. Pyloric dilator was given and pylorus stretched to 54 F.

May 7. Stomach washed out in the morning in the fasting condition showed no food remnants from the previous day; weight, eighty-eight and a half pounds.

May 13. Pylorus stretched to 55 F.

May 18. On ordinary diet; weight, ninety-two pounds.

In the table, as well as in the cases described, a distinction is made between pylorospasm and benign stenosis of the pylorus. The easiest way to ascertain which of the two conditions is present, is by measuring the pylorus. In pylorospasm No. 50 to 60 F. can be passed through the pylorus, while in real stenosis No. 40 F. is about the largest size that can go through at first.

Indications for stretching of the pylorus:

I. Stretching of the pylorus can be performed with advantage in all cases of pylorospasm, provided there is no fresh active ulcer in the pylorus or its immediate vicinity. If a fresh ulcer in this region is present, as evidenced by the thread test, a course of treatment should first be undertaken toward the cure of the ulcer. As soon as the thread test becomes negative, careful stretching of the pylorus can be undertaken. If, however, the ulcer shows no tendency to heal, or if there are frequent recurrences indicating exacerbations of the ulcerated process, an operation is indicated.

2. Beginning benign stenosis of the pylorus forms a large field for the treatment by stretching with the same exceptions as mentioned in Paragraph 1.

3. Advanced benign strictures of the pylorus, which cannot be operated: either on account of the great underlying danger, like heart lesions, kidney, or liver, complications, advanced old age, or when the patient absolutely refuses surgical intervention, can likewise be subjected to the internal stretching. In this group the usual pyloric dilator frequently fails to pass, while the dilating catheter over the thread is still able to occasionally enter the pylorus.

As already stated in one of my previous papers, the method of stretching of the pylorus is not antagonistic to surgery. It works hand in hand with it. Where one procedure fails or is unfeasible, the other steps in as its helpmate.

LARGE-CELL SPLENOMEGALY (GAUCHER'S DISEASE): A CLINICAL AND PATHOLOGICAL STUDY.

By N. E. Brill, M.D.,

ATTENDING PHYSICIAN TO MOUNT SINAI HOSPITAL; PROFESSOR OF CLINICAL MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY,

AND

F. S. Mandlebaum, M.D.,

PATHOLOGIST TO MOUNT SINAI HOSPITAL, NEW YORK.

Owing to the haze which surrounds the conception of medical men in reference to the subject of the Gaucher type of primary splenomegaly, the authors are prompted to make an attempt to show that this specific form of disease has little in common with a promiscuous group of diseases whose chief characteristic is an enlargement of the spleen. The subject has been still further confused by a recent article appearing in *Surgery, Gynecology, and Obstetrics*, March, 1913, by L. B. Wilson, who reports three cases of primary splenomegaly, Gaucher type, for which splenectomy had been performed at St. Mary's Hospital, Rochester, Minnesota. In the literature which he has considered for the preparation of his article, he assumes as authentic cases many of those belonging to the promiscuous group of splenomegalies to which we have just referred, and which writers who have given much time to an intimate study of this disease have justly eliminated. The reasons for their elimination have already been fully considered in the publications of Marchand, Schlagenhaufer, Risel, and others. We can see no clinical or pathological factors which might have justified Wilson in restoring to the list of proved cases of the Gaucher type those in which the verdict against their genuineness has been so unanimous.

There are varying conditions which are attended by splenomegaly. Some of these are plasmodial infections, syphilis, tuberculosis, amyloid disease, rickets, circulatory disturbances in the portal system, blood diseases (including the leukemias), Hodgkin's disease, and a large group, to which the French have particularly called attention, of associated hepatic cirrhoses of a hypertrophic type, with splenic enlargements. Unfortunately to many of these, and particularly to the group of splenic anemias, the term "primary splenomegaly" has been applied. We deem it desirable, therefore, to isolate from this group one form, whose picture is so distinctive clinically, and whose pathological process is so unique, as to merit an individual name. We would therefore suggest that this affection should be called Gaucher's disease, so as to avoid the use of the term "splenomegaly," which is only one of the features of the

disease, but which has occasioned much of the confusion to which we have alluded above.

DEFINITION. The characteristic features of Gaucher's disease are its incidence in childhood, its frequent presence in other members of the family of the same generation, a progressive increase in the size of the spleen which often reaches colossal dimensions, followed by a similar hugh enlargement of the liver, a characteristic brownish-yellow discoloration of the skin, usually restricted to the face, neck, and hands, a peculiar yellowish, wedge-shaped thickening of the conjunctivæ commonly seen on both sides of the cornea, and the prolonged and chronic course of the disease, which does not materially disturb the health of the individual. After the disease has been present for a considerable time there is a definite tendency to hemorrhages, especially appearing as epistaxis, bleeding from the gums, and ecchymoses in the skin following the slightest trauma. The positive finding in the blood, even in the early stage of the disease, is a definite leukopenia. The erythrocytes, however, show no definite change either in number, form, size, or hemoglobin content until the disease has existed for a long time, when an anemia of the chlorotic type makes its appearance. The anemia is rarely pronounced at any stage. The disease is not accompanied by palpable enlargements of the superficial lymph nodes. There is no jaundice and ascites is exceptional. The disease has none of the characteristics of malignancy, and usually is terminated by some intercurrent affection.

The pathological feature of the disease is the presence in the spleen, liver, lymph nodes, and bone-marrow of distinctive large cells, with characteristic cytoplasm and small nuclei. The enlargement of the spleen and liver is due to the presence of these cells in enormous number. In well-established cases all of these organs contain pigment giving the reaction for iron. Whereas the nature and origin of these cells are still moot questions, the histological picture is uniformly characteristic and pertains to no other form of disease.

ANALYSIS OF INDIVIDUAL SYMPTOMS. While there are no individual symptoms which are pathognomonic of this disease, we believe that a definite association of certain symptoms is sufficient to enable one to clinically diagnosticate its presence. It was this association of symptoms which enabled one of us to make the diagnosis clinically in two cases, which was subsequently confirmed by pathological examination. A detailed analysis of these clinical factors is justified owing to their importance. We shall, however, confine ourselves strictly to such cases as have been proved by histological examination of the tissues obtained either by autopsy or by splenectomy. We purposely shall not consider the cases occurring in brothers and sisters presenting the identical clinical picture as the affected member of the family, because absolute scientific confirmation is lacking.

The cases established under these conditions are: (I) Gaucher,[1] 1882; (II) Collier,[2] 1895; (III) Picou and Ramond,[3] 1896; (IV) Bovaird,[4] 1900; (V) Brill, Mandlebaum and Libman,[5] 1904; (VI) Schlagenhaufer,[6] 1907; (VII) von Herczel,[7] 1907; (VIII) Marchand,[8] 1907; (IX) Brill, Mandlebaum and Libman,[9] 1909; (X) De Jong and van Heukelom,[10] 1910; (XI) Mandlebaum,[11] 1912; (XII) Wilson,[12] 1913; (XIII) Downes,[13] 1913; (XIV) Erdmann.[14]

ONSET. In the large majority of cases the beginning of the disease cannot be determined, because it starts insidiously and is unattended by any subjective symptoms which might attract the attention either of the parent or the affected individual. After the disease has existed for some time and has given rise to a splenic enlargement, which in some patients may produce symptoms of discomfort or slight pain, it first begins to attract attention; in others, in the course of a physical examination for some other condition, which may have no relation to the disease itself, a splenic hypertrophy is discovered.

AGE. As a rule the disease begins in early life. Among the fourteen proved cases the age at which the disease was detected is as follows: Case I at seven years; Case II at two years; Case III at twenty-eight years; Case IV at three years; Case V at nineteen years; Case VI at five years; Case VII at thirty-three years; Case VIII at twenty-four years; Case IX at twenty-one years; Case X at seven and a half years; Case XI at three and a half years; Case XII at twelve years; Case XIII at thirteen years; Case XIV at one year. From this it may be seen that the disease appeared before the age of twelve years in the majority of cases and in infancy or early childhood in several instances.

SEX. Females are more frequently affected than males. In the fourteen reported cases the disease occurred in males only twice.

[1] De l'epithélioma primitif de la rate, Paris, 1882.

[2] Trans. Path. Soc. London, 1895, xlvi, 148.

[3] Bull. Soc. anat. de Paris, 1895, lxx, 531; Archiv. de méd. expér. et d'anat. path., 1896, viii, 168.

[4] AMER. JOUR. MED. SCI., 1900, cxx, 377.

[5] Proc. New York Path. Soc., 1904, iv, 143; AMER. JOUR. MED. SCI., 1905, cxxix, 491.

[6] Verhandl. d. deutsch. path. Gesellsch., 1907, x, 77; Virchow's Archiv. f. path. Anat., 1907, clxxxvii, 125.

[7] Wien. klin. Woch., 1907, xx, 127.

[8] MÜnch. med. Woch., 1907, liv, 1102.

[9] AMER. JOUR. MED. SCI., 1909, cxxxvii, 849.

[10] Beitr. z. path. Anat. u. z. allg. Path., 1910, xlviii, 598.

[11] Jour. Exp. Med., 1912, xvi, 797.

[12] Surg., Gyn., and Obst., 1913, xvi, 240. An examination of the slides which were kindly sent to us by Dr. Wilson revealed the undisputed existence of the disease in only one of his three reported cases. This conclusion was arrived at after careful and critical study. Our reasons for excluding two of his cases will be referred to later in the article.

[13] Med. Record, 1913, lxxxiii, 697.

[14] In a recent communication before the New York Surgical Society, J. F. Erdmann presented a spleen which he had removed from a child, aged three years and four months. A portion of the spleen was kindly furnished to us. It shows the presence of the disease in an early stage. An article reporting this case will be published later in the AMER. JOUR. MED. SCI.

Familial Occurrence. The disease often affects more than one child of the family. There seems to be no tendency to hereditary transmission, and in none of the established cases has any parent been affected. If one wishes to include those cases in the family, which from a clinical standpoint have the same symptoms as the individual proved case, then the familial character has been noted seven times. The authors who have mentioned such cases are Collier; Bovaird; Brill, Mandlebaum, and Libman; Schlagenhaufer; De Jong and van Heukelom; Mandlebaum; Erdmann.[15]

Enlargement of Spleen. The splenic hypertrophy is one of the important features of the disease. It is slowly progressive, occurs in every case, and gives rise to a distinct protrusion. The amount of abdominal and thoracic protrusion is in direct proportion to the increase in size of the affected organ. While at first the left side of the trunk is decidedly enlarged, with the subsequent increase in size of the liver, the anomalous one-sided protrusion becomes symmetrical. At the latter stage the trunk is definitely barrel-shaped, the lower part of the thorax joining in a distinct curve with the upper part of the abdomen. The time required for the spleen to reach colossal proportions may be many years. The size of the spleen is greater than that in any other disease, not even excepting leukemia. The upper border may be percussed even as high as the fifth rib in the axillary line, and the lower border not infrequently extends below the iliac crest into the pelvis, so that it cannot be felt by abdominal palpation. Anteriorly the rounded edge may be traced by palpation to the region of the umbilicus, where it often curves to the right, and may thus occupy the greater portion of the abdomen. The posterior border may often be felt in a line continued vertically from the angle of the scapula; occasionally it may even be felt along the vertebral column. At the umbilicus a distinct notch is usually felt, whose depth may admit three fingers. In some cases, however, more than one notch may be felt. The surface is usually smooth, even though a considerable amount of perisplenitis be present.

Enlargement of Liver. This seems to develop only after a considerable increase in size of the spleen has taken place. It gives rise to the uniform thoracic and abdominal protrusion referred to above. Its upper border may reach the fourth rib, and its lower border be felt 3 cm. below the umbilicus. Occasionally the splenic enlargement may so overlap the liver that the lower border of the latter can only be felt in the anterior axillary line and posteriorly. The surface is also uniformly smooth.

Skin. Early in the disease the skin of the face and neck, as well as the hands, presents a peculiar discoloration. It is usually spoken of as a pigmentation,[16] but we prefer to call it a discoloration,

[15] Personal communication.

[16] No histological examinations of the skin affected by this discoloration have as yet been made.

because it is uniform in distribution and intensity, and is limited to the parts of the body exposed to light. In one case only has this discoloration been noted on the abdomen. The color is a peculiar yellowish-brown (ochre). It frequently assumes a deeper shade across the bridge of the nose and around the eyes, and after the disease has existed for a considerable time the discoloration becomes uniformly more intense. Often the skin presents numerous ecchymoses, varying in size and color, because the superficial vessels are particularly susceptible to injury from the slightest trauma. Furuncles assuming a hemorrhagic character have been noted, which on healing have left definite and permanent skin lesions of a dark pigmented nature.

Some authors describe this specific discoloration as a jaundice or a subicteric tint. Our own analyses show an absence of bile in the blood and urine, with an excess, however, of urobilin in both. A tendency to general sweating associated with sudamina has been noted in a few cases.

Eyes. Early in the disease a change in the conjunctiva of both eyes may be noted. This manifests itself in a brownish-yellow, wedge-shaped thickening, affecting first the nasal side of each conjunctiva, its base being limited by the cornea. Later on the temporal side also becomes the seat of a similar thickening. The development and growth of these thickenings are very slow. They seem to originate near the corneal margin and extend in the process of growth to the inner and outer canthus respectively. They resemble in some respects the lesion of the conjunctiva known as pinguecula, and may reach dimensions of 3 mm. along the corneal margin and 5 mm. in length. We have never seen a case of the disease in which this peculiar ocular lesion was absent, and therefore again emphasize its diagnostic significance.

Hemorrhages. There seems to be a tendency in all of the cases to bleeding from the mucous surfaces. In most of the cases epistaxis is a frequent occurrence; in some cases this is associated with bleeding from the gums, which are often swollen and spongy. Melena and metrorrhagia have been observed. Attention has been called above to the occurrence of hemorrhagic furuncles and numerous ecchymoses in the skin.

Blood. An important positive factor is a leukopenia which appears early in the disease and persists throughout. As few as 500 leukocytes to the cubic millimeter have been noted. The average count of all the reported cases is 4600. The differential count, using the average of all the authentic cases, is as follows: Polynuclears, 66; small lymphocytes, 20; large lymphocytes, 13; eosinophiles, 1. In two cases myelocytes were found, 2 per cent. and 1 per cent. respectively. Mast cells were also noted in two cases, 0.8 per cent. and 0.5 per cent. respectively.

It is remarkable that notwithstanding the fact that the disease

involves the entire hemopoietic system, its effect on the blood-forming organs should be attended by so little demonstrable change in the morphological characters of the blood. The number of erythrocytes is not materially diminished until the disease has existed for some years. The red-cell count for quite a long period is close to normal. Later in the disease a diminution slowly takes place. In the advanced cases the average of all the reported counts is 3,700,000. As high as 6,000,000 red cells have been noted in one case. There seems to be a greater reduction in the hemoglobin content than in the number of the red cells, giving rise to a low color index, and therefore of a mild anemia of the chlorotic type. The appearance of the patient does not even suggest an intense degree of anemia, because the skin of the majority of patients does not show an inordinate amount of pallor, nor do their mucous membranes.

There is little if any change in the contour, shape, or size of the red cells. The color may be slightly paler than normal. In only two of the cases have nucleated forms been observed; in these a solitary normoblast was seen in each. Megaloblasts have never been noted. The large specific type of cell, the so-called "endothelial cell," whose presence in all the hemopoietic organs characterizes the disease, is never found in the peripheral circulation. The hemoglobin shows a reduction before the red cells suffer any marked decrease. Its average in all the cases reported is 65 per cent. As high as 92 per cent. and as low as 35 per cent. have been observed.

Lymph Nodes. The superficial lymph nodes of the body are not usually palpable. Where careful search is instituted, occasionally a few solitary lymph nodes in the axilla and in the groin may be felt as small, hard, pea-sized bodies.

Absence of Jaundice and Ascites. We have already directed attention to the peculiar brownish-yellow discoloration of the skin of those parts of the body which are exposed to light. This discoloration has been called jaundice by some writers. We insist that this is a misnomer, because bile pigment has not been found in the blood or urine. Ascites is almost invariably absent, even though the disease has existed for twenty-five years or more. In only one case has it been reported.

Symptoms Occasionally Manifest. After the spleen and liver have grown to a large size a few patients complain of abdominal pain, chiefly referable to the region of the spleen. This pain is not constant. It may be absent for many months before it is complained of again. During the period of pain, tenderness over parts of the spleen may be elicited. This would seem to be occasioned by the presence of local areas of perisplenitis. Pain and tenderness over the liver are only exceptionally present. The weight of the spleen and liver gives rise in a few patients to a sense of dragging discomfort in the abdomen. It is remarkable that not-

withstanding the colossal size of the spleen and liver, there is very little complaint in the majority of the patients referable to these organs.

Very late in the existence of the disease, only after many years, some patients direct attention to pain in the lower ends of the femur and tibia, and still later to pain and tenderness in the muscles of the thigh and calf. Bone tenderness over the sternum and tibia is absent.

A remarkable feature of this disease, to which we have already drawn attention, is the preservation of the feelings of comparative comfort and well-being which dominate the patient. As a rule, patients do not feel depressed, nor are their mental activities diminished.[17]

EMACIATION. Most of the advanced cases present a loss of adiposity. The appearance of the patient, with the tremendously enlarged abdomen and the emaciated frame, makes a striking picture. In one of our cases, a female adult, there was a total body weight of 89 pounds.

DURATION AND TERMINATION. The disease is essentially chronic; its course is slow and progressive. Schlagenhaufer's patient lived for thirty-six years after the disease was detected. The average duration of all the authentic reported cases where death has not resulted from splenectomy is 19.3 years. The disease is usually terminated by some intercurrent affection. A few of the reported causes of death are tuberculosis, pleurisy, and pericarditis. Operative procedure (splenectomy) has occasioned three deaths. Another case died as the result of an accident causing a fracture of the skull and laceration of the brain.

PATHOGENESIS. Much speculation has been indulged in to explain the nature and origin of this disease. When first described by Gaucher its nature gave rise to considerable discussion, and it was considered by some to be a form of malignant disease. Later writers, taking into consideration its clinical course, its long duration, as well as its histological features, have justly disproved this assumption. Various theories have been offered, such as the influence of an endogenous toxin, of an enzyme manufactured by the spleen, infection by protozoa, tubercle bacilli, and the like. No evidence has ever been presented which might substantiate any of these as causative factors. While it is true that a tropical form of splenomegaly, known as kala-azar, exists

[17] One of the patients now under observation, in whom the disease is known to have existed for at least twenty-four years, presenting a gigantic spleen and liver, which together almost completely occupy the entire abdominal cavity, is still able to attend to her household duties and social functions, and though forty-four years of age, still indulges in the summer in sea-baths, swimming, and tennis. This is one of a family in which four cases have occurred. The existence of the disease in two of these cases was confirmed by autopsy. We have purposely added this case in a footnote, so as to adhere to the plan expressed above, to include in our paper only the cases which have been proved histologically.

in which protozoa have been found, a thorough search for similar organisms has always failed. In the present state of our knowledge the confession must be made that we know nothing definite of the pathogenesis of this disease.

DIAGNOSIS. While the diagnosis of the disease in its early stage is well-nigh impossible, owing to the absence of associative symptoms, the fact that more than one member of the family may be afflicted with varying degrees of combined splenic and hepatic enlargements ought to suggest the possibility of its existence. When the disease has sufficiently developed, so as to give rise to a distinctly large spleen, even though but one member of a family be affected, the diagnosis, while difficult, may possibly be made. The factors which might enable one at this stage to determine the existence of the disease are the large spleen, a beginning hepatic enlargement, the conjunctival lesion, and the absence of anemia, jaundice, and ascites. Blood examinations must always be made, so as to exclude the possibility of a leukemia.

When the disease is fully developed the diagnosis ought to be possible in the majority of cases. The enormous enlargement of the spleen and liver; the brownish-yellow discoloration (non-icteric) of the skin; the conjunctival thickening; the long duration of the disease; its predilection for females; its familial occurrence; the feeling of comfort and ease, notwithstanding the tremendous protrusion of the lower thorax and abdomen; the tendency to hemorrhage, manifested by epistaxis and bleeding from the gums; the ecchymoses in the skin; the persistent leukopenia; the mild degree of chlorotic anemia without changes in the red cells; the absence of jaundice and ascites; the absence of palpable lymph nodes, make a symptom complex which differentiates this disease from the groups called splenic anemia and Banti's disease, with which groups it is most likely to be confounded.

While it is true that splenic anemia and Gaucher's disease have much in common, yet we believe, contrary to Hutchison,[18] that they are distinct and can readily be separated. The features common to both are the splenic enlargement, the chronicity of the affection, the hemorrhagic tendency, the absence of leukocytosis, and the anemia of the chlorotic type. The differential factors are the relatively shorter duration of the disease in splenic anemia; the pallor of the skin, which toward the end becomes distinctly jaundiced; the more pronounced type of the anemia, which occurs early and is a prominent factor in the disease; the feeling of distress and illness; the tendency to hemorrhages of a more generalized type, as expressed by frequent attacks of hematemesis as well as melena; the relatively smaller size of the spleen; the markedly smaller size of the liver; the absence of the conjunctival

[18] A System of Medicine, Allbutt and Rolleston, 1909, v, 759.

lesion, and the presence of ascites. These factors are so distinctive that in a large majority of cases the differential diagnosis between Gaucher's disease and splenic anemia may be established.

It was the recognition of these differential factors which enabled one of us (Brill),[19] De Jong and van Heukelom, and Reuben[20] to diagnosticate the presence of Gaucher's disease during life, which diagnosis was subsequently confirmed by histological examination in each instance.

The disease may be confounded with chronic splenomegalic acholuric jaundice, which likewise is a familial form of disease, and occurs in infancy and early childhood, sometimes hereditary, and is associated with anemia, with considerable enlargement of the spleen, and a moderate enlargement of the liver. The distinctive blood changes, such as fragility of the red blood cells, normoblastic and megaloblastic crises, and leukocytosis, would differentiate this from Gaucher's disease.

Hanot's disease is likewise characterized by its chronic course as well as by a large liver and spleen. Jaundice in this disease is an early symptom, and exists continuously in varying degrees of intensity. At any time during the course of the disease an icterus gravis may occur. The urine usually contains bile. Its course is generally attended by fever, which is rarely or ever present in Gaucher's disease. The hepatic and splenic enlargements are moderate as compared with the hypertrophy of these organs in Gaucher's disease. Leukocytosis is usually a prominent feature.

It would appear unnecessary to mention in this connection the possibility of mistaking leukemia, Hodgkin's disease, and pernicious anemia for Gaucher's disease. The characteristic blood picture and the enlargement of the lymph nodes in leukemia would immediately differentiate it, although the possibility of a stage of remission in leukemia with an approximately normal blood-count might be met with, when a differential diagnosis would be established with greater difficulty. Even under such conditions the marked pallor of the skin, the enlarged superficial lymph nodes, and the absence of leukopenia would suggest some other condition than Gaucher's disease.

The only form of Hodgkin's disease which would admit of the possibility of error in diagnosis is the splenomegalic form without enlargement of the lymph nodes. Such a form, however, is still a moot subject of discussion. The usual form of Hodgkin's disease, while it may present some enlargement of the spleen, is commonly associated with periods of fever and with greatly enlarged lymph nodes. A combined splenic and hepatic enlargement of colossal size does not occur in Hodgkin's disease.

[19] Amer. Jour. Med. Sci., 1901, cxxi, 377.
[20] Amer. Jour. Dis. Child., 1912, iii, 28.

The characteristic high color index, the definite changes in size and shape of the red-blood cells, together with the nucleated forms, the extreme degree of anemia, the color of the skin, the preservation of the adiposity, are sufficient factors in establishing the diagnosis of pernicious anemia, even though a moderate degree of splenic enlargement be present.

French authors, particularly Chauffard, Lereboullet, Gilbert and Fournier, and Gilbert, have described under the terms metasplenomegalic hypertrophic biliary cirrhosis, presplenomegalic hypertrophic biliary cirrhosis, hypersplenomegalic hypertrophic biliary cirrhosis, and a special juvenile type with great splenic enlargement, a medley of diseases whose existence has seldom been met with in any other country than France. The clinical history and pathological features of these forms are so involved, both in obscurity and chaos, and the characters which would entitle them to clinical entities are so meager and ill-defined, that it is possible some of these forms may have been examples of unrecognized Banti's disease or Gaucher's disease.

PATHOLOGY. The description of the pathology herewith presented is based upon the investigation and study of the material obtained post mortem in three cases, and upon the spleens obtained after splenectomy in two other cases, representing in stage of development, the early, the intermediate, and the late periods of the disease.[21]

The organs involved in Gaucher's disease are the spleen, liver, lymph nodes, and bone-marrow, all of which show the presence of peculiar large cells and a variable amount of iron-containing pigment. The large cells are characteristic and present the following features. They are usually round or oval in shape, but when seen in large compressed masses may assume a polygonal outline. The average measurement is from 20μ to 40μ in diameter, and a cell may contain from one to four or more nuclei of relatively small size. When smears are made from the freshly cut organ (Fig. 1), cells of hugh size may frequently be found.[22] The cytoplasm stains faintly with acid dyes and often presents a streaked and wrinkled appearance, but with high magnification a granular character may be noted. Some of the cells show vacuoles, probably the result of phagocytosis. Degenerative forms are not present excepting in cases of long duration, but in the liver the cells may be so fused that their individual outlines are not easily recognized. The nuclei are small, round, deeply staining, or, occasionally, somewhat larger irregular bodies. Rarely do the nuclei show atypical mitotic changes. Whereas the cells are quite unlike any found in other

[21] The ages of the patients from whom this material was obtained were three years, four and a half years, twenty-eight years, thirty-four years, and thirty-seven years.

[22] A cell of this type from the spleen measured 71.7μ by 100μ, and contained thirteen nuclei.

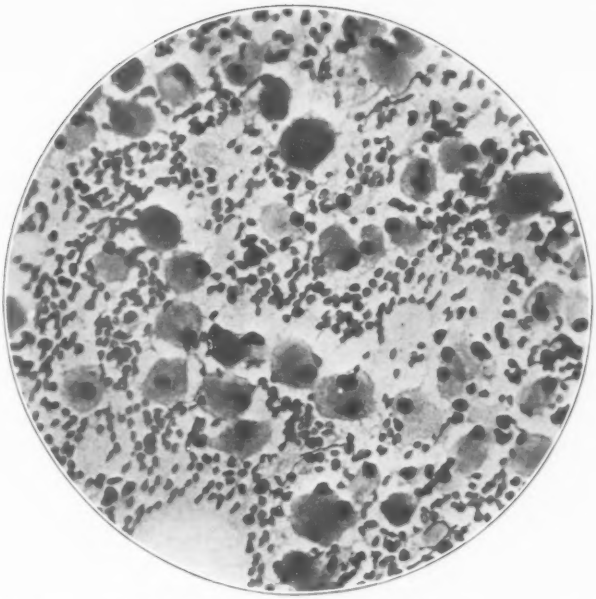


FIG. 1.—Smear from fresh surface of spleen. The size of the large cells as compared with the red-blood cells is readily appreciated. × 300

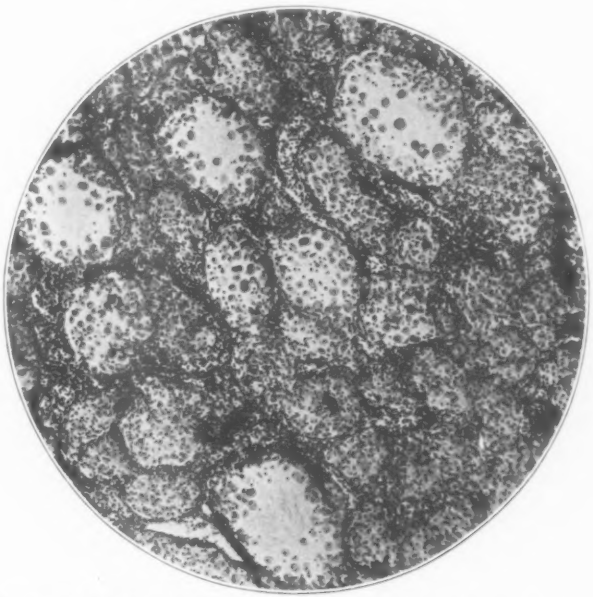


FIG. 2.—Section of spleen showing dilated venous sinuses filled with blood cells (not visible with low power) and large cells. Remainder of field composed of alveoli completely filled with large cells and separated by normal pulp cells. × 80.

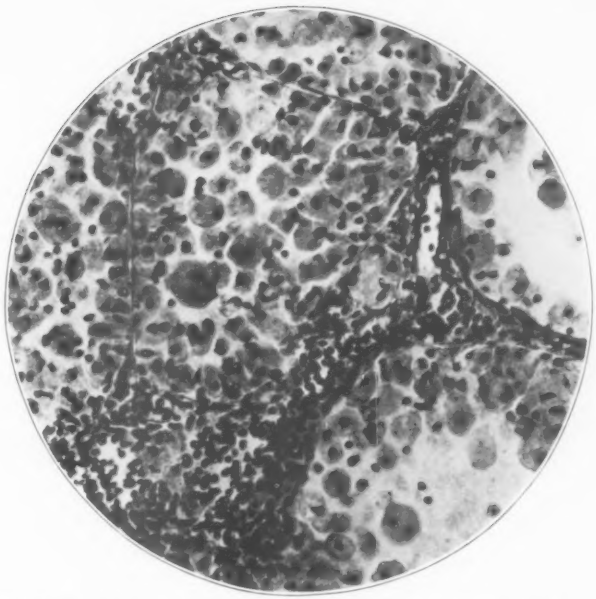


FIG. 3.—Section of spleen. On the right are segments of two sinuses containing large cells and red-blood cells. Connective-tissue septa between the alveoli are seen above and on the left. × 300.

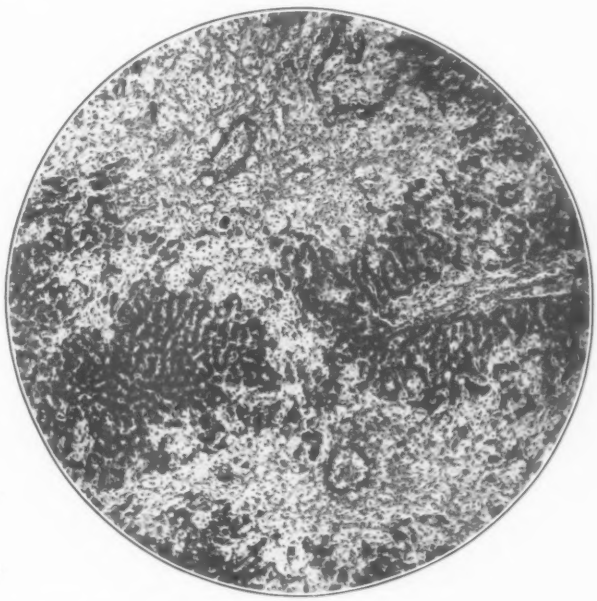


FIG. 4.—Section of liver showing the large amount of interlobular connective tissue. The large cells cannot be differentiated with this power. × 80.

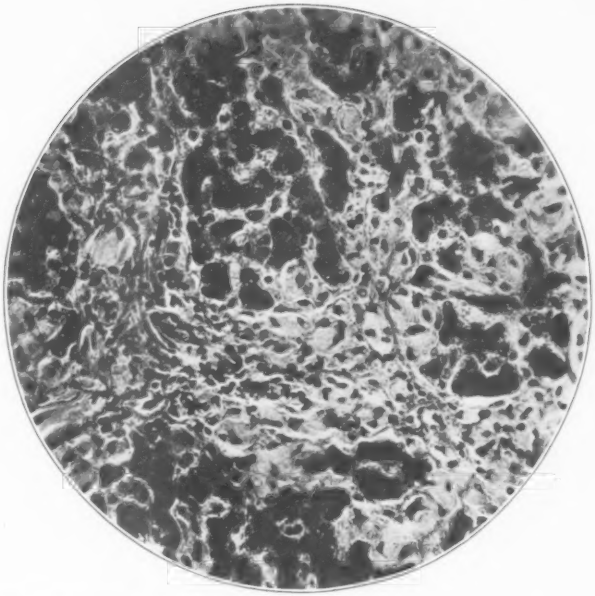


FIG. 5.—Section of liver showing large cells in the meshes of the connective tissue and in the sinusoids. The large cells are compressed and their outlines somewhat obscure. × 300.

FIG. 6.—Section of retroperitoneal lymph node. The large cells form distinct cellular masses, between which are seen strands of normal lymphoid cells. × 80.

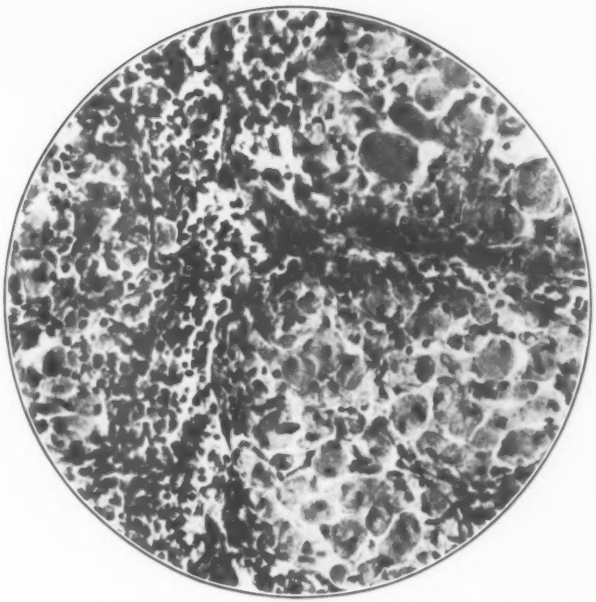


FIG. 7.—Section of same node, showing lymph sinuses filled with large cells whose outlines are clearly distinguished. × 300.

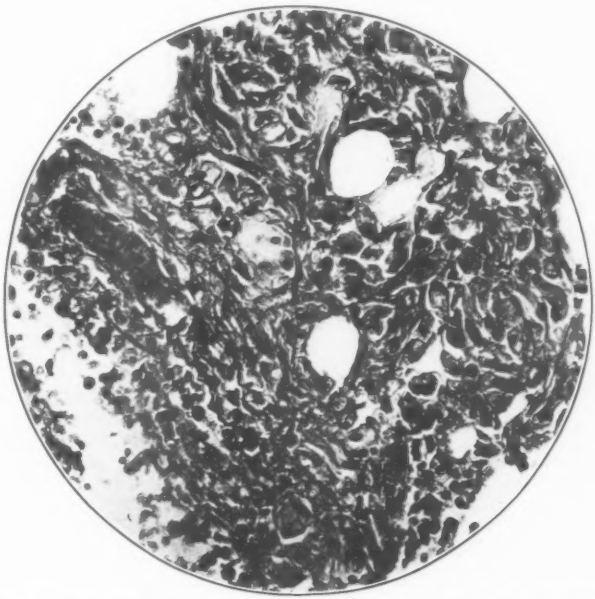


FIG. 8.—Section of bone-marrow from the tibia, showing compressed and distorted large cells. On the left and below are small groups of normal marrow cells. × 300.

pathological processes, one might compare them with atypical, swollen, and desquamated endothelial cells.

SPLEEN. This organ always retains the shape and general appearance of a spleen. The surface is perfectly smooth excepting in cases of long duration, when the capsule may be markedly thickened and rough, and show scattered areas of perisplenitis, as well as localized depressions due to infarctions. The color varies from brownish pink to brownish red. The cut surface is usually brownish red and often mottled with white or grayish streaks. The Malpighian bodies are not visible, nor can the trabeculæ be recognized. Minute hemorrhagic dots are frequently seen, and the infarcts when present are often surrounded by hemorrhagic zones. The splenic vein in adult cases may show slight sclerosis; it is frequently of hugh size.

The spleen varies in size and weight according to the duration of the disease. In one of our cases it measured 45 x 25 x 13 cm. and weighed 7400 grams (14 pounds 13 ounces), one-sixth of the entire body weight. The average weight in thirteen authentic cases (including the one of only 490 grams obtained from a child) was 3600 grams (7.2 pounds).

Microscopic examination shows that the normal splenic structure is replaced by large, round, or irregularly shaped, alveolar spaces, whose walls are formed by delicate connective-tissue fibres, distinctly lined by endothelium. These spaces represent the greatly dilated venous sinuses of the organ (Fig. 2). In all these spaces the characteristic large cells are seen, some lying free, others attached to the endothelium. Many of the sinuses also contain red blood cells. Sinuses are also seen, presenting the same general appearance and filled with large cells, but without definite endothelium (Fig. 3). A few normal pulp cells are usually found between the sinuses, also capillaries of normal appearance. Reticulum fibres cannot be detected within the sinuses. In most cases the follicles are few in number, and with the exception of a slight thickening of the walls of the central artery in long-standing cases, show no changes. In early cases, however, the follicles may be of enormous size. Scattered throughout the pulp are isolated groups of the typical large cells, and some of these large cells are usually seen between the lymphoid cells at the peripheral portions of the follicles. The germinal centres of the follicles in early cases show atypical lymphoid cells without mitotic changes, also large nucleated cells (phagocytes) containing Flemming bodies. Early cases may also show large cells resembling megakaryocytes, containing fused masses of deeply staining nuclear matter. Large hemorrhagic areas are not uncommon in long-standing cases, and pigment is invariably present. This is seen between the connective-tissue fibers of the trabeculæ, within the endothelial cells of the capillaries, and in many of the typical large cells. The pigment

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granules are brown or brownish yellow in color, and show the usual iron reaction. The early cases, however, show little or no pigment. In cases of long duration areas of degeneration may be found, but the contours of the large cells may still be recognized, as a rule. In two cases, Schlagenhaufer's and Erdmann's, areas of tuberculosis were observed. These we believe are only incidental and have no bearing or relationship to the diseased process.[23]

LIVER. In young individuals the surface is smooth and glistening; its color is a light yellowish pink. On section the same color is noted and the lobules are but faintly indicated. In the older cases the surface may be slightly uneven, owing to localized areas of perihepatitis with irregular thickening of the capsule. The color in these cases assumes a darker hue of brownish red. On section the parenchyma swells above the cut surface; its color varies from a brownish pink to a brownish red. A few grayish streaks and markings are often noted, but they bear no relation to the usual lobular outlines. Occasionally fine hemorrhagic points are seen. The size of the liver is invariably increased, and is in direct proportion to the duration of the disease. In one of our cases the weight of the liver was 4800 grams (10 pounds). The average in all adult cases where the weight of the liver was noted (five in number) was 3450 grams (7.2 pounds).

The noteworthy feature of the liver, microscopically, is the enormous amount of interlobular connective tissue, which gives the usual picture of a fibrosis when examined with the low power (Fig. 4). A more critical examination, however, shows that a great number of cells, identical in type with those found in the spleen, are situated in the meshes of the connective tissue. Many of these cells have lost the typical appearance, and individual cells cannot always be differentiated. They frequently appear as flattened or compressed and fused masses (Fig. 5). In the sinusoids, however, isolated large cells are found. These cells usually are well-preserved, but they are not directly connected with the reticulum fibrils which form a delicate net-work between the columns of liver cells. In the advanced cases most of the large cells in the sinusoids are situated near the peripheral portions of the lobules.

[23] At the 1912 meeting of the German Pathological Society, W. H. Schultze reported a case of diabetes, with marked lipoidemia, in a man aged twenty-seven years. The spleen, which was only slightly hypertrophied, contained large cells, in which Schultze found a distinct lipoid substance. No large cells were found, however, in any of the other organs. On account of the similarity of the cells to those found in Gaucher's disease, he calls attention to the possible occurrence of a lipoid substance in the latter. No fresh material being available, our observations to establish this fact could only be made on a portion of spleen fixed in formalin. We succeeded in obtaining a faint stain with Nile blue, but the results with the Fischler, Smith-Dietrich, and Ciaccio methods were not corroborative. A final decision as to the presence of a lipoid in the cells in Gaucher's disease should not be made until the various methods have been employed on frozen sections of fresh unfixed material, for Bell (Anatomical Record, 1910, iv, 199) has shown that formalin solutions often have a solvent action on lipoids, and the staining methods may give negative results in consequence of such fixation.

The individual liver cells are not apparently affected by the presence of the large cells, nor are any changes noted in them as the result of compression by the interlobular connective tissue. Occasionally the liver cells show a somewhat coarsely granular appearance, and in old cases minute fat droplets have been seen. None of the large cells in the liver appear to have phagocytic properties. In the early stages of the disease iron-containing pigment is absent, but in the more advanced stages it is always found, situated in the capsule as well as in the neighborhood of the smaller bloodvessels, but not in the large cells. The bile-ducts are not affected and appear normal, and no changes are present in the intralobular veins or in the branches of the hepatic artery.

In Schlagenhaufer's case numerous miliary tubercles were found in both lobes of the liver. We do not believe that they have any direct relationship to the disease.

Lymph Nodes. In noteworthy contrast to the usual absence of enlarged superficial lymph nodes, those in the thorax and abdomen are always increased in size. The mesenteric, retroperitoneal, and iliac lymph nodes, also the nodes at the hilus of the liver and the spleen, and those in the region of the pancreas, are enlarged in early cases. They measure from 0.5 cm. to 2. cm. in diameter, and are usually soft and friable. The color is brownish gray or reddish gray or a bright red, or the surface may be pale and the central parts deep red. The bronchial lymph nodes are also enlarged and present a similar color.

In advanced cases the abdominal and thoracic lymph nodes are also increased in size, but to a relatively less degree than in children. In our own cases none of the nodes exceeded 2 cm. in diameter. The color varies from yellow or ochre to dark red, and in very advanced cases the nodes may be brownish black. The yellowish nodes may show hemorrhagic markings on section.

Microscopic examination in the advanced cases shows the presence of the typical large cells, extensive fibrous changes, a large amount of pigment, and a diminution or entire absence of lymph-adenoid tissue. The large cells are frequently present in such enormous numbers that the picture of a glandular organ is commonly absent. The connective-tissue framework is intact, however, and an occasional follicle or a small remnant of lymphoid tissue may still be preserved here and there (Fig. 6). Notwithstanding the presence of large cells in such abundance, the individual cell bodies are clearly and distinctly outlined, and fusion of cells is rarely seen in the lymph nodes. The large cells are found also in the lymph sinuses (Fig. 7). The capsule is often greatly thickened and the trabeculæ very prominent, giving the appearance of a fibrosis. The large cells appear to have a definite relationship to the reticulum and to the endothelium of the lymph sinuses. The pigment is dark brown in color, crystalline or amorphous in char-

acter, and always gives the reaction for iron. It is distributed throughout the node, but is most abundant in the sinuses under the capsule and along the trabeculæ. Pigment crystals are often found in the large cells, giving evidence of their phagocytic properties.

The lymph nodes in the early cases show variations in the degree of involvement. Some groups present an involvement which may be as far advanced as in the adult cases; other nodes may show the lesion in an earlier stage. In our last case, a boy, aged four and a half years, the iliac, mesenteric, retroperitoneal nodes, and those at the hilus of the liver, presented an older type of lesion than the bronchial and pancreatic nodes or the nodes near the splenic vein. The general picture in the advanced lesion in children is identical with that described in adult cases, but the capsule and trabeculæ are less prominent, and pigment is absent. The follicles may show great hypertrophy of the germinal centres with much cellular activity, as evidenced by active mitosis in the lymphocytes. Eosinophile myelocytes may be found in these nodes in considerable number.

The nodes presenting an early type of lesion may appear quite normal with low magnification. The typical large cells are seen, however, if a more critical examination be made, and they can be found in the lymph sinuses and here and there between the pulp cells. The follicles are quite prominent, and in the germinal centres phagocytic cells containing remnants of red-blood cells and pigment may be noted. In our case a small amount of pigment was found in all of the nodes showing the early type lesion, but in the nodes about the splenic vein it was very prominent. It appeared as rounded granules of yellow or brownish color and was alwasys situated in large cells which bore a striking resemblance to the typical large cells of the disease. Remnants of red-blood cells were also present in these phagocytic cells, side by side with the pigment granules. A close relation of reticulum and large cells could be seen in these nodes. Eosinophile and neutrophile myelocytes were present, also a few polymorphonuclear cells with eosin granulations.

Bone-marrow. The lesion in the bone-marrow was first noted by us in 1904, twenty-two years after Gaucher's first description of the disease. The color of the bone-marrow is always red, and small white or yellowish areas may be present. The consistency, as a rule, is soft. The typical large cells are found either singly or in groups, and no characteristic variation in the degree of involvement between early and advanced cases is apparent. At times the large cells may be seen in extensive groups, and in such situations considerable distortion of the cells may result from compression (Fig. 8). Reticulum fibers are present between the cells, and a close relationship between the two exists. Some of the large cells show vacuoles, but no distinct phagocytes are seen. Pigment

is present in small amount, but only in cases of many years' duration, and is found in the vicinity of the larger bloodvessels. Small areas of normal lymphoid tissue may be discovered in the early cases. Those portions of the marrow not involved show normal cells, including myelocytes of all types, eosinophile and neutrophile leukocytes, normoblasts and megakaryocytes.

OTHER ORGANS. In many of the cases a considerable degree of hypertrophy has been found in the lymph-adenoid tissue of the lower ileum and cecum, also marked pigmentation in the muscle fibers of the intestine. In Schlagenhaufer's case fine pigment granules of a yellow color were seen in the muscular tissue of the uterus, and marked perivascular pigmentation was noted in several normal organs, including the salivary glands. The thigh muscles in Marchand's case were the seat of hemorrhages and pigmentation, with an active new formation of striated fibers.

Although the large cells typical of the disease are found only in the hemopoietic system, it is noteworthy to mention that Risel[24] reports finding some of these cells in a connective-tissue septum of the thyroid gland in Marchand's case. Inasmuch as a small collection of lymphoid cells was seen nearby, one may reasonably assume that the latter represented misplaced lymph-adenoid tissue in which the large cells had their origin.

TREATMENT. This paper would be incomplete if no reference were made to the treatment of the disease. Before splenectomy came into vogue as a remedial measure, attempts at cure had been made by drugs, chief among which was arsenic in its various forms administered by mouth and hypodermically, and local injections into the spleen of methylene blue and pyoktanin. None of these agents seemed to have any influence upon the progress of the disease, nor did they produce any amelioration in the condition of the patient. The only effect of the *x*-rays applied to spleen and bones was to temporarily reduce somewhat the size of the spleen without arresting the disease.

It is too early to give judgment upon the value of splenectomy. While the blood seems to regain some of its normal elements, such as the increase in the number of red and white cells and the amount of hemoglobin, we cannot say how permanent this change may be. Of the 8 splenectomies performed among these 14 cases, 3 died as a result of the operation. Of the remaining 5, no report has been made, so far as we know, by Picou and Ramond or by von Herczel in reference to the subsequent history of their cases. In De Jong and van Heukelom's case, however, the liver continued to enlarge. The cases of Downes and Erdmann have so recently been operated that the signs of improvement which at present are manifest may be only temporary. It would seem to us that a disease which is

[24] Beitr. z. path. Anat. u. z. allg. Path., 1909, xlvi, 241.

not confined to the spleen, but involves all the organs of the hemopoietic system, could not be materially stayed in its progress by the removal of but one member of this system. However the future must decide. Inasmuch as more improvement has resulted from splenectomy than from any other measure it is our duty to recommend this operation and to insist that it be performed as soon as the disease is suspected.

Discussion. Were it not for the fact that an extensive literature pertaining to the subject of Gaucher's disease has been steadily accumulating, containing reports of alleged cases based on meager observation, insufficient symptomatology, and uncorroborated by histological examination of any tissue, the authors would have deemed their work concluded without further discussion. But many of these cases which have found a position in this literature ought to be, once and for all, removed. While the original reporters of some of these have not diagnosticated their individual cases as belonging to the Gaucher type, subsequent commentators have included them in the list, chiefly because they were of familial type and had large spleens and anemia.

Among those most frequently cited are the following: Weichselbaum,[25] Harris and Herzog,[26] Rolleston,[27] Borissowa,[28] Springthorpe and Stirling,[29] Stengel,[30] Umber,[31] O'Malley and O'Malley,[32] Cowan,[33] Rettig,[34] and Plehn.[35] In their original contributions, Borissowa, Stengel, Rettig, and Plehn described their cases as belonging to the category of Gaucher's disease.

Borissowa's case has occasioned considerable study and discussion, and has been analyzed by Marchand, Askanazy, Schlagenhaufer, Risel, and De Jong and von Heukelom. These authors are not unanimous in their opinions as to the exact nature of her case, but they are agreed that it does not belong to the Gaucher type. The cells are much smaller, the cytoplasm has entirely different characteristics, and the nuclei are much larger than in Gaucher's disease. Naegeli,[36] who examined the blood, called attention to the presence of megalocytes, megaloblasts, and the high color index, as well as marked leukocytosis and 3 per cent. of myelocytes.

Through the kindness of Dr. Stengel we had the opportunity in 1905 of studying the sections in his case, and concluded that they

[25] Virchow's Arch. f. path. Anat., 1881, lxxxv, 562.
[26] Ann. Surg., 1901, xxxiv, 111.
[27] Clin. Jour., 1902, xix, 401.
[28] Virchow's Arch. f. path. Anat., 1903, clxxii, 108.
[29] Lancet, London, 1904, ii, 1013.
[30] Amer. Jour. Med. Sci., 1904, cxxviii, 497.
[31] Zeitsch. f. klin. Med., 1904, lv, 289.
[32] Amer. Jour. Med. Sci., 1905, cxxix, 996.
[33] Quart. Jour. Med., 1908, i, 11.
[34] Berlin. klin. Woch., 1909, xlvi, 2046.
[35] Deutsch. med. Woch., 1909, xxxv, 1749.
[36] Blutkrankheiten und Blutdiagnostik, 1908, 401.

presented no histological evidences in common with our own. This conclusion was also reached by Ledingham,[37] who says that Stengel's case cannot be included "in the category either of Banti's disease or the Gaucher type of splenomegaly."

Rettig's one case (the daughter) showed, in addition to a moderate enlargement of the spleen and liver, and a discoloration of the skin, the presence of enlarged cervical, axillary, and inguinal lymph nodes, and a decided leukocytosis, the latter features being uncommon to Gaucher's disease. His other case (the father) presented a similar picture, though the lymph nodes were not enlarged. Plehn's cases represent a disease occurring in two generations, father, son, and daughter. Both Rettig's and Plehn's cases have been diagnosticated on purely clinical grounds. They have many points of similarity with the clinical picture of the disease, and we shall await with interest subsequent communications which may substantiate their diagnoses.

Weichselbaum's case lacks all clinical data, and its histology is very meager. If a conclusion could be reached from his facts, one might suspect that his case represented an endothelial sarcoma, an opinion which Risel also entertains.

Harris and Herzog's first case was subjected to a splenectomy. From the histological examination one is not justified in including it in this group. Marchand, Schlagenhaufer, and Risel, independently, have expressed doubts as to its genuineness.

Rolleston at no time intimated that his case was one of Gaucher's disease. In his clinical lecture on splenic anemia he incidentally discusses the subject of Gaucher's disease, without even hinting that either of the two cases therein presented were anything else than splenic anemia.

Springthorpe and Stirling's cases belong to one family and appear in two generations. On account of the familial occurrence alone, some authors have included them under the group of Gaucher's disease. Their clinical data are insufficient for this conclusion. Splenectomy was performed upon two of them, but the reports of the histological examination are lacking in detail and insufficient to justify the diagnosis.

In the case reported by O'Malley and O'Malley the spleen diminished 10 cm. in size while under observation, the liver also became reduced in size, ascites was present, and a moderate grade of leukocytosis was noted. The patient died after splenectomy. The liver showed atrophic cirrhosis without "unusual endothelial proliferation;" the spleen had none of the characteristics of Gaucher's disease.

Umber stated positively that his first case was one representing an early stage of Banti's disease. On this account we cannot

[37] A System of Medicine, Allbutt and Rolleston, 1909, v, 773.

understand how any writer could have included it under Gaucher's disease. Having read his clinical history and the report of the histological findings in the spleen and liver, we can find no evidence to disprove Umber's own diagnosis of Banti's disease. Umber's second case, a seventeen-year-old boy, who had sixty-four liters of ascitic fluid removed during a period of four months, finally recovered. Umber states in his paper that his original diagnosis of Banti's disease was incorrect, and that the disease was probably a thrombotic process in the branches of the portal vein following scarlet fever.

Cowan was unable to classify his cases, stating that they resembled cases of splenic anemia in infancy. A perusal of his communication does not support in our minds the conclusion of other writers who have placed them in the group of Gaucher's disease.

We regret to see that Wilson, who is one of the latest contributors to the subject of Gaucher's disease, has included in his three cases two which admit of the most serious doubt. The author himself asserts in his article that one of his cases is quite identical with Stengel's case. He describes in the third a colloid degeneration as a later process of the disease. Wilson's first case (No. 8869) is a typical example of Gaucher's disease. The second case (No. 9315), like Stengel's, shows an enormous amount of connective tissue, mostly arranged in bands encircling the venous sinuses. The large cells seen in the sinuses show branching forms lacking the more or less rounded contours seen in other cases, and the nuclei appear relatively large, though we admit that this appearance may be due to shrinkage. Giant cells resembling the Langhans type are present in large numbers. These are seen in the sinuses and also between the lymphoid cells. The resemblance to a tuberculous lesion is most striking, even though distinct tubercles are not seen. In none of the other cases have giant cells of this variety been encountered in the sinuses. In a few of the cases isolated multinuclear cells described as "giant cells" have been observed, but there is no recorded case excepting that of Stengel in which giant cells of the Langhans type have been found in such profusion. For these reasons we do not believe this case to belong to the category of Gaucher's disease. Wilson's third case (No. 58,571) has no resemblance whatever to any lesion described as characteristic of Gaucher's disease. The sections show enormous spaces (sinuses) filled with a homogeneous, faintly granular material, giving the impression of a circulatory disturbance with stasis and resulting exudation. It is true that in a few situations, particularly in small sinuses under the capsule, large desquamated endothelial cells are found, but this is not uncommon in many forms of splenic hypertrophy due to various causes.

Having given an exposition of the constituent factors of Gaucher's disease, there still remains the consideration of the views of various

authors as to the origin of the characteristic large cells and the nature of the pathological process. Briefly summarized these are as follows: Gaucher believed that the disease represented a primary epithelioma of the spleen. Collier concluded it to be an endothelioma. The Morbid Growths Committee who examined his slides denied the sarcomatous nature of the process. Picou and Ramond thought the disease represented a primary epithelioma, non-malignant at the beginning, which was converted later into a malignant process, which subsequently involved the lymph nodes. Cornil, who discussed this case, expressed the opinion that it was a primary hypertrophy of the spleen with proliferation of the reticulum.

Bovaird regarded the disease as "a hyperplasia of the spleen, characterized by an unusual development of endothelial cells and the transformation of a considerable part of the organ into dense connective tissue." He likewise considered the lesion in the lymph nodes and liver to be an endothelial hyperplasia, confined in the liver to the lymph spaces in the perilobular connective tissue. He suggests the likelihood of "the action of some systemic poison affecting several members of a family."

Brill, Mandlebaum and Libman thought that the large cells arose from endothelium or normal reticulum in the hemopoietic apparatus, and suggested a peculiar susceptibility of these structures to some unknown toxic agent. They stated that tuberculosis, when found in these cases, must be considered as a superimposed process.

Schlagenhaufer stated that the large cells could be readily differentiated from the endothelial cells and did not arise from them. He considered the process to be a systemic disease of the lymphatic-hemopoietic apparatus, with proliferation of the reticular structures, affecting the spleen primarily, then the regional and other lymph nodes, and finally the liver and bone-marrow. For a time he thought that the tuberculous lesions were secondary, but finally decided that some toxin, probably of a tuberculous nature, but without other manifestations of true tuberculosis, was the most likely etiological factor.

Von Herczel considered the spleen to be the seat of an inflammatory process or a new growth. The histological examination was made by Krompecher, who confessed his inability to explain the complicated picture. Risel subsequently examined the slides and found the typical picture of Gaucher's disease. This diagnosis was accepted by Krompecher.

Marchand was of the opinion that the cells might have their origin either from reticulum or endothelium, and that they contained some unknown substance of a peculiar homogeneous, amyloid nature, with the properties of some form of semi-solid hyaline material. Risel, after a more detailed study of the material in Marchand's case, concludes that while there is no positive proof that

the cells arise from reticulum, and no transitional stages between reticulum and cells can be observed, nevertheless he believes the reticulum must be their seat of origin. He also states it is his belief that in the lymph nodes the cells may arise from the endothelium of the lymph sinuses, late in the course of the disease, as well as from the reticulum within the follicles. He admits that the presence of the cells in the venous sinuses of the spleen is difficult of explanation, assuming that they originate in the reticulum. He concedes that the cells are carried to the capillaries of the liver through the protal vein, but he acknowledges his inability to explain their presence in the connective-tissue spaces of Glisson's capsule.

De Jong and van Heukelom concluded that the cells arise from proliferated reticulum, but could not deny the possibility of an endothelial origin. They believe that the cells have the power of multiplying, because they found peculiar cells undergoing direct cell division in the spleen, and because the liver continued to enlarge after splenectomy in their case.

Mandlebaum thought that the large cells might be derived from large lymphocytes or reticulum cells in the germinal centres of the follicles, and described the phagocytic cells found there. The large cells are carried through the portal vein to the liver, and he believes that their destruction in this organ causes an irritation leading to the production of the connective-tissue process.

Downes calls attention to the extensive, uniform, diffuse, endothelial hyperplasia, and says that the cells "resemble those seen in the so-called 'large-celled hyperplasia' of lymph sinus endothelium."

Wilson considers the process to be a "primary endothelial proliferation with a secondary proliferation of fibrous connective tissue, and ultimately a degeneration of the endothelium with contraction of the connective tisse." He concludes that the large cells are "much more likely to have arisen from the endothelium than from the reticulum."

From the above opinions it may be seen that while all are agreed as to the histological features of the lesion, the source and nature of the cells are still wrapped in mystery. We recognize the fact that neither an origin from reticulum alone nor endothelium alone will explain the pathological features in all the organs. Neither will the theory of an origin from large lymphocytes or reticulum cells in the germinal centres of the follicles explain all of the lesions. It has been shown by Rössle and Yoshida[38] that no differentiation between reticulum and endothelium, especially in lymph nodes, can be made. Therefore it is possible that in the lymph nodes at least the large cells may arise from both of these structures.[39]

[38] Beitr. z. path. Anat. u. z. allg. Path., 1909, xlv, 110.

[39] A full discussion of the various factors concerned in the attempted explanation of the pathogenesis of this disease is to be found in the original articles of Schlagenhaufer, Risel, De Jong and van Heukelom, and Mandlebaum.

We believe that the disease starts simultaneously in the spleen, bone-marrow, and lymph nodes. In the last, however, it may appear somewhat later or be slower in development, an assumption which finds its support in the fact that we have found in a very early case, a child aged four and one-half years, the process in some of the nodes to be far less advanced than in the spleen and marrow.

If in this communication we have succeeded in giving a place in nosology to what appears to us to be a distinctive clinical and pathological entity we shall be satisfied. This satisfaction would be the more complete and our object more fully accomplished, could we hope that in the future all the cases which lack the distinctive features of the disease would be excluded from the literature.

NOTE.—Since the above was written, with the kind permission of Wilson, the slides of his three cases were submitted to Marchand for an opinion. Marchand writes that Wilson's first case is a typical splenomegaly of the Gaucher type. He agrees that the second case is one of tuberculosis, even though tubercle bacilli could not be demonstrated in the sections or by animal inoculation. The third case, he says, looks like a lymphangioma, although small collections of cells, seen under the capsule, resemble somewhat those found in Gaucher's disease. A study of these cells in the fresh state would be necessary, however, before giving a final opinion as to the nature of the lesion.

ADDENDUM.—An opportunity to examine fresh unfixed material for the presence of lipoid substance has been afforded since this paper has gone to press. Through the courtesy of Dr. E. P. Bernstein we have just obtained from the pathological laboratory of the Lebanon Hospital a piece of spleen removed at operation from a case of Gaucher's disease. Tests with the polariscope, as well as examination of frozen sections stained with Nile blue and Sudan III are negative, thus indicating the entire absence of neutral fat, cholesterin, and cholesterin esters from the large cells in this disease. Chemical studies for the purpose of extracting lipoids from the spleen are now in progress.

METALLIC POISONS AND THE NERVOUS SYSTEM.[1]

BY GEORGE A. MOLEEN, M.D.,

NEUROLOGIST TO HOSPITAL OF THE CITY AND COUNTY OF DENVER, MERCY, AND ST. JOSEPH'S HOSPITALS, ETC., DENVER, COLORADO.

THIS subject is presented not so much because of being anything especially out of the ordinary, for many of the things which will be mentioned may have been known to some, but one fact that I feel sure is, as is well stated by Gowers, the commonplace of all knowledge, that which we can least afford to despise or to disregard.

In a recent number of *Everybody's Magazine* appears a popular (if not also somewhat exaggerated) article entitled "The Lead Menace," by Gordon Thayer, in which the author endeavors to show the importance of the passage of the Occupational Disease Bill, introduced in several State legislatures at the instance of the

[1] Read before the Medical Society of the City and County of Denver, Colorado, April 1, 1913.

American Association for "Labor Legislation" for the protection of workers exposed to lead perils. In studying the many cases in the literature the great variety of nervous manifestations is found to be quite remarkable.

With these ideas in mind supplying a feeling of justification in doing so, I will first briefly present three cases, showing the effects of lead intoxication, one of arsenic and one probably of mercury, upon the nervous system, and later draw from the literature a few observations concerning this subject.

CASE I.—C. W. S., aged fifty-three years, painter by occupation, was first seen August 15, 1908. He came to Colorado two weeks previsously on account of rheumatism. The family history was negative. Other than the ordinary diseases of childhood, he had jaundice at nineteen, rheumatoid pains at twenty-four, and malaria at thirty-nine years. Four years before he had a severe attack of colic, with vomiting and dysentery. Gonorrheal infection was admitted and syphilis denied. Used alcohol occasionally, and at times to excess. Five months prior, following the taking of a cathartic, a lot of clear blood and clotted blood was passed, also some blood in the urine. This has occurred since. The patient complained of increasing weakness in the arms and shoulders, with considerable pain. There had been no absolute loss of power. Otherwise the health had been good. On examination he appeared anemic; was 5 feet $8\frac{1}{2}$ inches in height, and weighed 136 pounds. The muscles of the shoulders, arms, and forearms were symmetrically wasted, and the eminences of the hands diminished. Power was much diminished and the right arm could only with great difficulty be brought to a horizontal position. Dynamometer (inner scale, Tiemann): R., 120; L., 180. He is right-handed. Tremor was absent in the hands, but a fibrillary twitching was evident in the deltoid and pectoral muscles. All coördinate movements were well performed, and the deep reflexes were all present and equal. All extensor muscles of the arm and forearm, as well as the supraspinati and infraspinati, showed a diminished faradic response, while prompt contractions were obtained in the flexors of the arm and forearm and the anterior shoulder muscles. The tongue was coated and the breath foul. A bluish-black line was to be seen at the margins of the gums in the upper and lower jaws.

The case was regarded as a muscular atrophy, and due to chronic lead intoxication. The absence of the wrist-drop or extensor paralysis was noteworthy, but the usual predilection of the extensors was evident in the diminished faradic responses, Of interest also was the occurrence of pain, for which he had been advised to come to this city, with the belief that it was rheumatic. Whether or not the bleeding from the bowels and kidneys was a result of the high vascular tension so common to lead could only be inferred. The usual eliminative treatment, with massage and stimulation, by

increasing doses of strychnine and iron to overcome the anemia, resulted in sufficient improvement to permit of resuming work in

FIG. 1.—Case I, showing atrophy of the spinati.

FIG. 2.—Case I, showing atrophy of arm including the deltoid.

a few months as a wood finisher, avoiding lead, but a complete recovery of the atrophy was hardly to be expected.

CASE II.—T. N. D., aged sixty-five years, painter by occupation, was referred in January, 1910, by Dr. Packard, on account of pain in the left arm and in the fingers, accompanied by numbness in the thumb and forefinger of the left hand and pain in the right leg. A year previously he experienced pain in the left arm and wrist, and believes it was weaker at that time. The family history contained nothing of importance, and other than that he had chills at twelve years, he had not been ill until three years previously, when he was treated for lead poisoning and had colic for about a year. Drank moderately, but never to excess; denied venereal infection.

On examination he appeared fairly well-preserved and of fair color. There were no paralyses and no wasting; muscular power was good. Dynamometer: R., 215; L., 180. He is right-handed. Facial action was present and equal. The tongue was protruded mesially. The margins of the gums of the lower jaw, and to some extent of the upper, showed a distinct bluish-black line.

The right knee-jerk failed in response even on reinforcement, while the left was present. The forearm reflexes of the left side were not as prompt as on the right. Both plantar reflexes were flexor. The right abdominals were less active than the left. Electrical reactions were normal. No sensory disturbance could be made out, other than slight hyperalgesia in the left forearm. Ocular motion was normal, and there was no nystagmus. Pupils were equal and responded actively to light and distance. The right fundus appeared normal, while the left appeared atrophic and presented some small hemorrhagic spots in the retina.

A neuritis, with perineural hyperemia and attributable to plumbism, was believed to be present, and the ordinary treatment was followed by prompt recovery. The absence of the right knee-jerk may have been attributed to the same cause, being distinctly unilateral, with a strong probability of being correct.

While the following case presents one of the more common effects of lead intoxication but also unilateral in type, there were associated circumstances which were misleading:

CASE III.—The patient was a housewife, aged forty-eight years, and had a negative family history, with the exception of a brother who died of tuberculosis, and a sister who became paralyzed at fifty-two years. Had no illness of consequence until two years previously, when a complete hysterectomy was done. About five months after operation, numbness of the right arm was noticed; this was accompanied by weakness, and she would drop things from the hands. There was no pain and she seemed to recover completely.

She was first seen January 27, 1913, and about ten weeks pre-

viously had fallen, striking and injuring the right knee, for which a cast was applied for three weeks. The patient was about on crutches for four or five weeks, when the right arm became numb, and loss of power was noticed. Otherwise she was in good health.

Examination revealed an anemic-appearing woman of good development, who presented a loss of power of the extensors of the arm, forearm, and hand, giving rise to the classic wrist-drop. The deltoid was unaffected and the supinator was likewise free. A fine lateral tremor of the fingers of both hands was present, but no tremor of the tongue. Grasp as indicated by dynamometer: R., 20; L., 180. She was right-handed.

There was total inability to extend the arm, and the hand likewise could not be extended. No sensory loss could be made out. The deep reflexes were normally present and equal, except the forearm extensors and the triceps jerk, which were much diminished.

There was a slight lateral nystagmus on extreme rotation of the eyes. Otherwise the external ocular muscular movement was normal. The fundi showed no change and the pupils were equal and responsive. Fields of vision were not contracted. Hemoglobin, 80 per cent. (Dare).

At the dental margins of several teeth a bluish-black line was to be seen, while it was absent over many others.

While one would think of a crutch paralysis in this case, the fact that the extensors alone, and especially the exception of the supinator, served to exclude this cause. Again, the first attack of paralysis and numbness, from which she had recovered, antedated the use of crutches.

Inquiry revealed the fact that prior to the paralysis there had been considerable painting done throughout the home, quite a lot of white lead was used, and the patient herself had done a great deal of the painting, and had frequently handled the lead.

The eliminative course of treatment, followed by stimulation and massage, and the exercising of the muscles by electricity, was followed by prompt return of power.

The following case presented an unusual effect of what appeared to be arsenical intoxication:

Case IV. — N. A., aged thirty-four years, a brother of a physician, was referred by Dr. Melville Black, December 22, 1911, on account of optic atrophy. Family and previous history negative. Venereal infection was denied, and alcohol as well. A great deal of Paris green had been handled in combating insects on potato vines. The patient was in direct contact with it, and, at times, his eyes would smart, while at other times, the backs of his hands would blister after handling it. After breathing the dust he would occasionally have a "funny feeling in the nostrils."

On January 15, 1911, double vision was noted which continued

a few months, and then disappeared. About two months before examination the vision of the left eye began to blur, and three weeks previously the right eye, especially on the temporal side, became affected, and the vision of both eyes have progressively failed since. Other than the failure in vision he was perfectly well. No tremor was noted. The patella and Achilles reflexes were absent, and there was some slight unsteadiness in gait and station. All other reflexes were about normal and equal. Sensation was present in all forms.

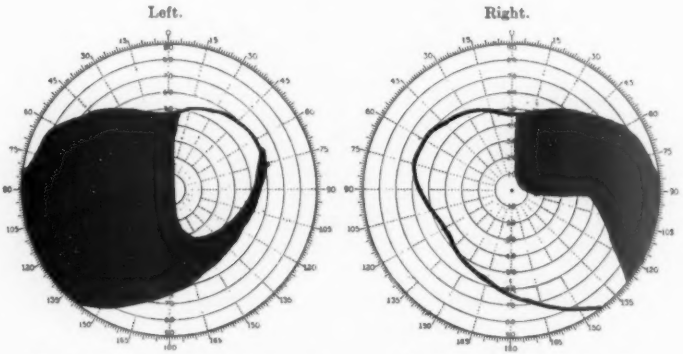

FIG. 3.—Case IV. December 22, 1911. O. D. V., $\frac{20}{30}$; O. S. V., finger in nasal field.

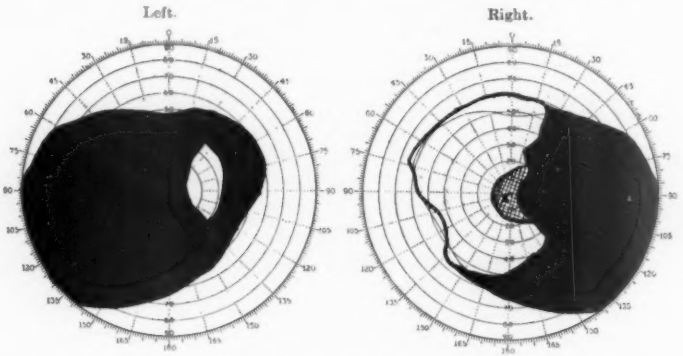

FIG. 4.—Case IV. January 26, 1912. O. D. V., eccentric, too weak to estimate; O. S. V., almost nil. Relative scotoma at *x*.

March 8, 1912. Dr. Hillkowitz reported the blood reaction as showing a Wassermann positive (Bauer-Hecht). The eyes showed no muscular impairment. Pupils were equal and responded to light and distance, the left less promptly than the right. Vision: R., eccentric, with central relative scotoma; L., almost *nil*. Fields

(see chart) showed a segmental blindness on the right and a small area on the left. Fundi: R., retina appeared normal—disk, marginal degeneration on the temporal side; lamina cribrosa quite marked; L., marked attenuation of vessels, disk distinctly atrophic, greenish white in cast; marginal degeneration on the temporal side. Hearing: $\frac{24}{24}$ in either ear. Aërial conduction greater than bone. A subsequent report from this case indicated the rapid progression of the blindness, which was then quite complete. Later, in view of the bilateral temporal blindness, the sphenoid was explored with

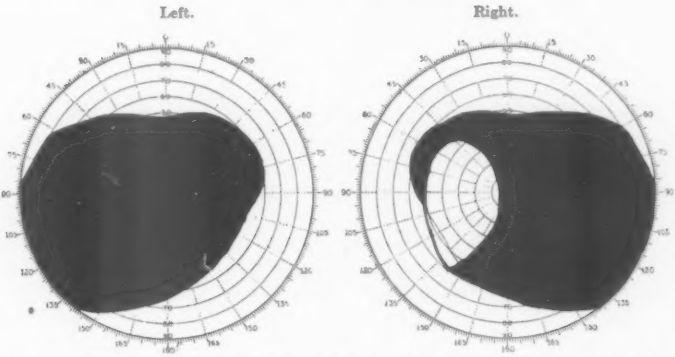

FIG. 5.—Case IV. February 28, 1912. O. D. V., eccentric; O. S. V., shadows in nasal field.

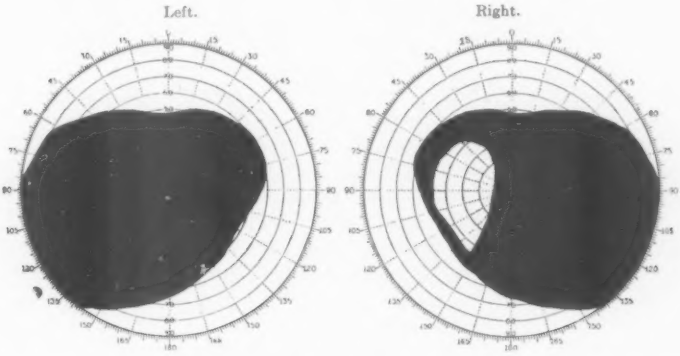

FIG. 6.—Case IV. March 12, 1912.

negative findings, and a skiagram showed no enlargement of the sella turcica nor evidence of pituitary growth. Here we have an unusual effect of arsenic, and I think we are justified in the conclusion that it was due to this metal, rather than to syphilis, tabes, or general paralysis for the following reasons: (1) A negative

history of venereal infection (Wassermann reaction is of questionable value in metallic poisonings); (2) direct exposure to arsenic, with history of what was undoubtedly arsenical dermatitis; (3) rapid progression of degeneration without neuritis; (4) segmentation of visual field not distinctly quadrantic, rather than concentric diminution; (5) retention of pupillary response to light; (6) the absence of subjective or objective sensory disturbance.

Case V.—W. C., aged forty-six years, a refiner of concentrates. Family history negative. He had been treated for various symptoms, but his history of specific infection was open to question.

In 1901 he began to notice numbness in the soles of both feet; this disappeared under iodide of potassium. Then followed dull, aching pains in the calves of the legs. Just prior to the onset he had been engaged in roasting mercury amalgam and the room was filled with the fumes of the mercury. There had been no girdle sense and no urinary difficulty. There was but little unsteadiness in gait, and no ataxia could be made out in the arms. The knee-jerks were absent on both sides, as was also the ankle-jerk. No tremor was to be seen in the tongue, and but slight tremor in the hands. No change in tactile, thermic, pain, or other senses was noted. The pupils were equal, and responsive to light as well as distance. There was no muscular deviation. Vision was $\frac{20}{20}$ in either eye. Disks were both normal. This case was believed to be a mercurial neuritis, and this view was strengthened by the fact that on several occasions he was given mercury because of suspected tabes or syphilis, and each time the neuritis became notably aggravated.

Rare Clinical Manifestations. The foregoing cases indicate the variability not only in the effects of the metallic poisons upon nerve structures, but carry at the same time the suggestion of an increased susceptibility in some individuals to their action. It is indeed remarkable what a variety of nervous disturbances have been found to be attributable to lead, and it is safe to presume there are many in which this cause has been overlooked.

Aside from the gastro-intestinal symptoms, high blood-pressure, and the more common extensor paralysis as a result of peripheral nerve lesion, there are affected at times, cranial nerves, giving rise to isolated paralyses, such, for example, as the cases of laryngeal paresis reported by O. Séifert,[2] who cites three cases resulting from lead poisoning. In the first case there was paresis of the arytenoideus proprius in a joiner, aged nineteen years, who had just recovered from lead colic. The second case, a varnisher, who had repeatedly suffered from lead colic, and was affected with saturnine nephritis, which resulted in edema. On laryngoscopical examination the mucous membrane over both arytenoid cartilages appeared

[2] Berlin klin. Woch. No. 35. Abs. Periscope, Jour. Nerv. and Ment. Dis., 1884, p. 694.

edematous; the vocal cords even in deep respiration remained nearly stationary, the left vocal cord approximating the median line a trifle more than the right one. In phonation the vocal cords approached each other, but failed to make their normal vibrations. The edematous parts were scarified, and after the reduction of the edema the hoarseness completely disappeared. The left vocal cord, however, remained nearer the median line on deep respiration. After death from uremia, beside other changes, the post-crico-arytenoid muscles were found to have undergone pronounced atrophy. In the third case all the interior laryngeal muscles of the right side were completely paralyzed, lead colic a year previous had been followed by repeated attacks of hoarseness; no pulmonary or lymphatic affections were evident.

Mosny, Dupey-Dutemps and Saint-Girons[3] report a blindness of twenty-four hours' duration, occurring after a homonymous hemianopsia for a like period, complicated with a pronounced state of torpor and intellectual weakness, which disappeared with the hemianopsia. The authors believe these should be added to the group of visual disturbances originating in lead paralysis, characterized by the sudden appearance of blindness, with conservation of the pupillary reaction, absence of lesion of the fundus of the eye, and a return of vision in a short time. The optic symptoms are believed to have been due to arterial spasm, localized in the occipital region, as a result of lead intoxication.

In 1880 M. Ernest Gaucher[4] reported a case of a house painter, who afterward engaged in the manufacture of white lead, who was suddenly seized with lead colic. On recovery he returned to work, but in two days fell unconscious. He presented the typical blue line, the lead constipation, and severe headache. Special senses were normal. Appetite was preserved. No albuminuria. Followed by delirium and vertigo; the cephalalgia continued. Shortly afterward he awakened aphasic and agraphic. Intelligence, sensibility, and motility were completely preserved.

In 1883 John J. Putnam[5] read a paper referring to the simulating of other diseases to lead poisoning; one case resembled lateral sclerosis: one, the transient forms of poliomyelitis anterior; two others a more diffused form of poliomyelitis, while both were cerebral neuroses.

That a distinct ataxic form of neuritis may occur and also present sensory phenomena was shown in those cases reported by Tedeschi,[6] who states that pseudotabes of saturnine origin is little known. Three observations are given, showing that in saturnism the ataxia is readily localized in the lower extremities, while in the paralytic

[3] Bull. et Mém. de la Soc. Méd. des Hôp., 1911, p. 620.
[4] La France Médicale, June 26. Abs. Periscope, Jour. Nerv. and Ment. Dis., p. 735.
[5] Trans. Amer. Neur. Assoc., Jour. Nerv. and Ment. Dis., p. 466.
[6] Il Tommasi, March, 1911, vi, No. 8, 177 to 183.

and atrophic forms it is the rule that the upper extremities are involved. There were sensory disturbances with two of his cases and none in the third.

The mind may be affected, and the literature is replete with cases showing melancholic, maniacal, confusional, and delirious states. In this regard, Kraepelin[7] states that the known poisonings are of considerable importance as developing among the occupational diseases. Mercurial poisoning not infrequently occurs in miners, makers of mirrors, and also in conditions associated with antiluetic cures we find mental difficulties, with marked irritability, timidity, perplexity, confusion, delusion, alarming dreams, and sleeplessness. Upon this ground, also, various forms of excited conditions or a gradual loss of psychic functions may develop—mental weakness and judgment, mental dulness, and loss of willpower. Those observed especially in painters, founders, and typesetters, the encephalopathia saturnina follows the acute course of lead delirium, with marked disturbance of consciousness, delusions, blunting of the consciousness, persecutory ideas, suicidal tendencies, etc.

They may even closely resemble the clinical picture of general paralysis, as the case of Delmas and Barbé,[8] who presented a patient affected with nervous and mental troubles having their origin in lead poison, and quite similar to those of general paralysis. The diagnosis rests upon the previous occupation, paraplegia, and the slow evolution of the symptoms, while certain symptoms of general paralysis were absent, such as the Argyll-Robertson pupil, absence of lymphocytosis, and a negative Wassermann reaction in blood.

Acute cases are few, according to Cowles,[9] who considers that painful, disabling affections and arteriosclerosis are in the majority.

Etiology. It is often difficult to ascertain the source of the poison, and especially since, as not infrequently occurs, very small amounts derived from little suspected sources are found to be responsible. Lewin[10] has seen symptoms of lead poisoning from merely a single shot, which had lodged between the teeth, as a woman was eating an apple. Another like case with optic neuritis and finally a brain affection and death, in which the poisoning was traced to the lead-foil wrapping of snuff, of which the young woman consumed 10 grams per day for months.[11]

Duckerling[12] found that inhalation is the principal source of trouble. The vapor of lead chloride is continually given up from the tinned articles for some time after removal from the bath.

[7] Psychiatrie, eighth edition, i, 100.
[8] Soc. de psych. de Paris, Rev. Neurol., 1911, p. 720.
[9] Boston Med. and Surg. Jour., September 5, 1907.
[10] Archiv f. klin. Chir., Berlin, xciv, No. 4.
[11] E. Stadler, Correspondenz-Blatt f. Schweizer Aerzte, February 10, xlii, No. 5.
[12] Jour. Hyg., London, September, 1908.

PATHOLOGY. Grave degenerations of the tracts and forms of pseudotabes have been met with in all three forms of metallic intoxications. Likewise, mental diseases have been directly traced to them after excluding other possible causes.

Mosny and Malloizel[13] summarize 47 cases of lead poisoning, with more or less involvement of the meninges. A latent histological meningitis seems to be almost constant in persons recently intoxicated by lead, and they believe it always accompanies lead colic. It may suggest the clinical picture of general paralysis, but differing in the absence of dementia, and by occasional recovery.

René Vincent[14] states that lumbar punctures systematically done in certain saturnine cases have disclosed the existence of a leukocytosis of the cerebrospinal fluid. This is not constant, is absent in old intoxications, and in the course of peripheral nerve lesions especially, this lymphocytosis, which occurs either independent of nerve symptoms or with the characteristic symptoms of meningitis, is collected under the name of saturnine meningitis, and it is stated that it most often follows immediately in the course of the lead colic.

DIAGNOSIS. The diagnosis of lead paralysis ordinarily presents little difficulty if the characteristic extensor paralysis without sensory symptoms and a bluish or dark line at the margin of the gums is encountered, and especially easy if the occupation is one which has to do with the handling of the metal and with a history of attacks of colicky pain and obstinate constipation.

Where these are not to be obtained and for the early detection of saturnism, Frey[15] offers the following means of detecting characteristic blood changes. The blood is dried, fixed with absolute alcohol, and colored with Loeffler's stain. In a certain number of red cells, the granules are colored blue.

It was previously stated that the Wassermann reaction could not be relied upon in cases of lead poisoning. Field[16] reports that in twelve cases of lead poisoning in which a Wassermann reaction was done it was positive in eight cases and negative in four.

Likewise, Schnitter[17] found four positive Wassermann reactions in sixteen cases of lead poisoning, and three of the four, he states, were free from syphilitic taint.

The elevation of blood-pressure was studied by Vaquez,[18] who believes the variations to be more important than the absolute figure. The rise during paroxysms was 50 to 100 mm.

Arsenical poisoning is more often associated with sensory disturbances than is lead, and a mixed paralysis involving the four extremities is the rule.

[13] Revue de Méd., June, 1907.
[14] La Méningite Saturnine, Thèse de Paris, 1910, No. 56.
[15] Deutsch. med. Woch., February 7, 1907.
[16] Jour. Amer. Med. Assoc., lviii, No. 22, 1681.
[17] Deutsch. med. Woch., xxxvii, No. 22.
[18] Sem. Méd., 1904, xxiv, No. 48.

Case IV is very unusual, and I have, in the limited literature at my disposal, been so far unable to find an optic nerve atrophy attributable to arsenic. The absence of sensory disturbance, while not usual, would seem in this case to negative the spinal degenerations commonly associated with primary optic atrophy. However, there can be but little doubt as to the cause in this, and that the loss of the knee-jerk was due to the same cause is probable. The absence of pigmentation of the skin is rather unusual.

Mercurial poisoning is not quite so common in its chronic form, but like lead and arsenic, perineural degenerations with evidences of peripheral nerve affections are in the majority.

Oppenheim compares the tremor of mercurial poisoning to that of disseminated sclerosis. Gowers describes the lateral tremor of the fingers as peculiar to lead. I have seen nystagmus in lead in the presence of other neurotic affections.

It should be stated with reference to the classic "blue" or "blue-black" line that it may or may not be present, according to the condition of the gums. It should be remembered that if it is present it is due to the fact that there is a separation of the gums from the teeth; that the line is due to the deposit of lead sulphide, and the sulphur is the result of decomposition of albuminous substances at this site. It may show, therefore, only over several teeth, over a great many or be entirely absent; but if distinct and at the margin, it should be considered as important evidence. It is probably not often blue, but more often black, and one gets the impression of blue, probably, from the red border of the gums; but whether blue or black is of minor importance, it is always a dark discoloration, and if at the margin of the gums, while it may not be conclusive, it should be regarded as strongly suspicious. Personally, I cannot recall another condition in which such a dark discoloration is present.

TREATMENT. In the treatment, iodides are used because of its effect in increasing the solubility in the blood, but a new danger arises, as was pointed out by Gowers, who cautions against the too free use of iodine, since the influence upon nerve structures is largely through the blood, and the throwing of a large quantity of the metal suddenly into the circulation may aggravate the symptoms.

Magnesium sulphate has long been known as a favorite eliminant. Calcium permanganate ($\frac{1}{4}$ gr. t. i. d.) is recorded to be of value by Stephens.[19]

A curious procedure recorded is the fixation abscess, which resulted in marked improvement, induced by V. Hinze[20] by subcutaneous injections of turpentine, 1 c.c. and 0.089 per cent. metallic lead recovered from abscess in 1.528 grams of pus.

[19] British Med. Jour., May 14, 1910.

[20] Berlin. klin. Woch., June, 1910. No. 26.

The same precaution regarding the free use of iodides obtains in the treatment of chronic arsenical intoxication as with lead.

CONCLUSIONS. In closing, one may draw a few points from the observations, such as: 1. A wide variation exists in individual susceptibility to all metallic poisons.

2. In those susceptible, if the nervous system is attacked, the peripheral nervous system is the most vulnerable, and more especially the extensor supplies.

3. There is with lead poisoning, in all probability, an early lymphocytosis of the cerebrospinal fluid, and probably coincident with, or succeeding upon, the basophilic granulation of the red blood cells.

4. Non-inflammatory degenerations of any portion of the peripheral system should suggest the metals as a possible cause.

5. In the absence of skin evidences of arsenic and the blue line of lead, the urine, the blood, and finally artificial abscesses may be induced and examined for the metals; this procedure should, it would seem, lend itself as a diagnostic as well as a therapeutic aid.

6. A positive Wassermann reaction would not seem to exclude, especially lead, in favor of syphilis in primary nerve or tract degenerations.

7. The source of the poison may not be detectable until long after the presence of the metal as a cause, has been established.

I desire, in conclusion, to express my indebtedness to Dr. Melville Black for his valuable aid in studying the visual fields and the preparation of the perimetric charts which have been used.

THE METABOLISM, PREVENTION, AND SUCCESSFUL TREATMENT OF RHEUMATOID ARTHRITIS: SECOND CONTRIBUTION.[1]

BY RALPH PEMBERTON, M.S., M.D.,

PHYSICIAN TO THE HOSPITAL AND DIRECTOR OF THE DEPARTMENT OF CLINICAL CHEMISTRY IN THE PATHOLOGICAL LABORATORY, PRESBYTERIAN HOSPITAL, PHILADELPHIA.

IN a previous communication[2] the writer advanced an hypothesis as to the general nature of rheumatoid arthritis, so called, and presented some metabolic and clinical observations upon three cases treated upon this basis. The tentative views there presented have been subjected to fuller consideration and development, and, in their application to a series of seventeen cases, form the substance of this paper. It may be well to repeat here some of the premises already stated:

[1] Reported before the American Association for the Advancement of Clinical Investigation, Washington, D. C., May 5, 1913.

[2] "The Metabolism and Successful Treatment of Chronic Joint Disease (Preliminary Report), AMER. JOUR. MED. SCI., October, 1912.

"It is a familiar clinical fact that chronic joint troubles form one of the most frequent and rebellious of diseases. The application of laboratory methods to the diagnosis of the several varieties and the rational treatment dependent upon it have reduced many of these to categories which are fairly well understood and yield good results. Thus the tuberculous, Neisserian, and specific joints tell their own story, but after eliminating them there remains a large class in which but little progress has been made. This is the class grouped by various writers under the headings, rheumatoid arthritis, chronic articular rheumatism, arthritis deformans, and so on, conditions having in common an obscure or doubtful etiology and a prognosis for the most part unfavorable.

"The activities of certain workers, particularly perhaps Goldthwaite and his collaborators in this field, have brought some order out of chaos, but it should be noted in passing, and with no credit to the internists and laboratory men, that it remained for orthopedists to suggest the simplest classifications and to practise the most rational therapy. It is due chiefly to the above men, for example, that we recognize in these obstinate cases the importance of a focus of infection in a tooth or tonsil, and that regulation of the diet along broad and intelligent lines is of value in the undernourished and overfed."

Lane, of London, has claimed that some of these cases are benefited by resection of the colon, but how or why this is beneficial is not clear. The matter will be referred to later.

"Grouping these cases as a whole, however, and eliminating them in turn from consideration, there remains a large and distressing number of cases which progresses from bad to worse despite all efforts.

"The principles of treatment as outlined above are now generally observed and practised by careful clinicians, but that they often fail is well known.

"The necessity of treating a number of sufferers from these conditions convinced the writer of the desirability of some definite observations by clinical and laboratory methods from which an etiology and treatment could be deduced.

"It is advised by many, for example, that in the dietary supervision incidental to good hygiene consideration should be had as to constipation, flatulence, the caloric need of the thin individual and the caloric surfeit of the fat individual, and that only the digestible foods should be eaten, that abundance of water should be ingested, and the like. At last analysis, however, these instructions are too generic, and in application fail of their purpose.

"The writer has observed in a number of instances the beneficial effect of purgation and starvation upon the subjective symptoms of certain joint cases, and the question is raised as to whether this be due to the absence of food decomposition and synthesis, to a diminution of intestinal bacterial activity, or to both. That the

amount of food *per se* is an important factor apart from its relation to bacterial activity is indicated somewhat by the well-known favorable action of arsenic in these states, one action of which is probably to hasten the general metabolic processes. Another agent capable of this same action, though to a greater degree, is thyroid extract, whose gradual effect on nitrogenous exchange and the persistence of this after administration of the drug has ceased, are testified to by many observers."[3]

On the basis of the reports of Lane and the not infrequent association of enteroptosis with joint disease, many have regarded the intestinal tract as related to this condition, but the manner of association has not been demonstrated.

Dietary control has been attempted in nearly every conceivable way, and has always failed, for the reasons to be later advanced. It is a conservative statement to say that, with the exceptions above noted, there has been to date no known successful therapy for arthritis deformans, and were any proof of this needed it could be found in the histories of most of the many sufferers from this disease, and, in particular, in the previous medical histories of cases here presented:

"It is plain, therefore, that a great reduction of the food intake, or the administration of agents which hasten the general body metabolism act beneficially on the symptoms of these conditions. The last mentioned agents, furthermore, are often beneficial even in conjunction with little or no reduction of the ingestod food and may even stimulate the appetite to a greater consumption. If we apply the reasoning here suggested it would seem likely that there is a point at which one or all of the elements of food can be assimilated with satisfaction to the body needs and without detriment to any particular structure.

"Having found such a dietary regimen there would be offered thereby an opportunity for study of the processes active for good and evil which might yield facts of value. Why such a study has not been attempted before is not clear to the writer, since opportunity has at times presented in those cases which have yielded to the correction of intestinal ptoses.

"Reference to the literature, however, indicates that while the contributions to chronic joint diseases have been legion, they have rarely been along the lines indicated, and have rarely been accompanied by careful laboratory studies.

"The lesson to be learned is in some respects like that taught by gout and diabetes, though the particular elements harmful in joint disease must yet be determined. An effort was made along these lines, beginning with the simplest of foods in order that the effect of their several component elements might more clearly be observed."

[3] Von Noorden, Metabolism and Practice of Medicine, iii, 991.

Milk suggested itself, of course, as the basis of experimentation, and was largely used in the first four cases treated. Owing, however, to the fact that the first case was that of a private patient, to whom buttermilk had been successfully administered, a complicating factor was introduced by adhering to it in the next three cases. The results were satisfactory clinically, but the issue was clouded by the introduction of the question of the intestinal flora. Suffice it at this point to say that subsequent experimentation and metabolic observations showed this to be an entirely unessential factor. The facts elicited by this study and their interpretation can probably best be approached by a recital of the series of cases.

Cases I, II, and III, with certain metabolic findings, have already been published (loc. cit.) and are not here included. Case I remains well (November, 1913). Cases II and III have disappeared from observation.

Case IV.—Mrs. X., aged about thirty-eight years; mother of two healthy children. Referred by Dr. James E. Talley. This patient presented an unimportant previous history apart from the present illness, which began about four years before admission, and had progressively involved the hands, elbows, shoulders, knees, and feet. She had tried a variety of treatments, and had been told by her regular physician, who sent her to Dr. Talley, that he could do no more for her. There were soft tissue swelling and deformity of the hands, wrists, knees, and feet, and the patient complained of much disability and pain, especially at night. This awoke her frequently, and prevented her turning or assuming different postures. Her general physical examination was negative, as were also her blood, urine, and blood pressure, and on admission her weight was 140½ pounds. At no time had she fever. *X*-ray[4] examination of her abdomen showed the head of the colon to be low in the pelvis, and the colon to be elongated, ptosed, and kinked. The stomach was also dilated and ptosed below the crest of the ilium. There was some demonstrable arthritis of both hands and slightly more of the elbows.

November 3, 1912, she was placed under the following regimen:

6 A.M.: 1 glass of buttermilk.

Breakfast: 2 apples; 2 pieces of toast and butter; 1 glass of buttermilk.

9.30 A.M.: Colonic lavage, with 2 quarts of normal salt solution.

10.30 A.M.: 1 glass of buttermilk.

Dinner: 1 orange; 1 bowl of tomato soup; 2 glasses of buttermilk; lettuce and tomatoes.

3.30 P.M.: 1 glass of buttermilk.

Supper: 1 piece of toast and butter; stewed fruit; 1 glass of buttermilk.

8.30 P.M.: 1 glass of buttermilk.

Aromatic fluidextract of cascara sagrada at bedtime.

[4] Dr. W. S. Newcomet made all the *x*-ray plates and interpreted the findings.

November 5. The caloric value of her food approximated 1748 calories, which was about 12.5 calories per pound of body weight,[5] or 27.5 calories per kilo body weight. She was given an option of spinach, celery, or tomatoes for the mid-day vegetable. The notes of her condition and dietary follow:

November 7. The stewed fruit was ordered given without sugar.

November 8. The improvement which had been suggestively present for two days was definite. She had no pain the previous night in her right shoulder nor in the neck for the first time in ten weeks. Did not feel stiff on waking. Hands were less sore and fingers could be moved more freely. Skin was somewhat wrinkled over the knuckles of the hand.

November 10. Apparently worse yesterday, as she had a poor night, but seemed better again. Fingers seemed more flexible than at any time yet. Complained of pain in the muscles along the shaft of the right arm and around the shoulder. Some "slip" and grating of right shoulder. Slight nausea complained of. Said her feet gave her no pain at all.

November 24. No pain for several days. Stiffness and soreness still on waking. Better than at any time since a gastric upset ten days ago. Walked entirely freely. Tongue was cleaner. Had a good night the last two nights.

November 29. Patient weighed 137½ pounds; felt well enough to leave the hospital, and did so, but resumed rather strenuous domestic duties in the care of her children. Furthermore, she lived at a boarding house, and careful adherence to or observation of her diet was no longer possible, though she did the best she could.

December 1. Could button her children's shoes better than formerly, and her husband noticed that the swelling has gone from her hand.

December 3. Weight, 142¾ pounds, dressed.

December 7. Relatively, the left hand was worse.

December 12. Not so well or at least no better. Conditions of life were not as salutary as at the hospital.

December 23. Weight, 142¾ pounds. Walked fairly well and said she had had pretty good nights, with occasional exceptions. Fingers were rather stiff, but were not much swollen. At this point she disappeared from observation.

Comment upon this case will be made later.

Case V. — W. S., aged seventeen years, rather slightly built, a student of illustration, was referred by Dr. F. H. Klaer. Admitted November 24, 1912. The patient had been treated at the dispensary of the hospital of the University of Pennsylvania for about three months without any substantial benefit. About four months previously, in July, he began to have stiffness and pain in a number of joints, which progressed from one to another until the right shoulder, both elbows, ankles, knees, and the fingers

[5] Pounds have been used in weighing patients, as the hospital scales were so graduated.

of both hands were involved, making it difficult or impossible for him to use a pencil. The middle phalanges of all the fingers were swollen and broadened, but, in general, the bony change was not marked. He put his coat on slowly and with difficulty, because of the stiffness of the shoulders, and complained of considerable pain at night. In June, 1912, he had an attack of tonsillitis, which kept him two weeks in bed, but he apparently recovered entirely from it. Three weeks later, however, the result above noted occurred. At the University of Pennsylvania Hospital dispensary search was made for a possible focus of infection, and, in line with this, his tonsils were removed without benefit. The boy was intelligent and presented no obvious errors of hygiene. He was the holder of a number of championships with the rifle, and had always been active physically. The urine, blood, and blood pressure were normal. The *x*-ray examination of the abdomen showed the large bowel to be elongated and doubled on itself, with a kink in the splenic flexure. The caput coli was lower than normal. The hands showed a marked inflammatory arthritis, with slight atrophic and hypertrophic changes.

This case was deemed a suitable one in which to study the metabolism during illness and convalescence, as in Case III (loc. cit.). He was accordingly put on a "metabolic" diet of known value, and instructed to decide how much food he desired and then to adhere to it. After a few days of probation he settled down to the following: Breakfast, dinner, and supper were identical, and consisted each of bread, 64.5 grams; 1 egg;[6] rice, 125 grams; butter, 9 grams; sugar, 10 grams; salt, ½ gram; milk, 200 c.c.; water, 800 c.c. per diem. This dietary was continued for twelve days, and examinations were made with respect to the following: Nitrogen of the urine; ammonia of the urine; chlorides of the urine; ethereal, preformed, and total sulphates of the urine; depression of the freezing-point of the urine (△); titratable acidity of the urine and the nitrogen of the feces.

The figures for the respective days follow later, and will be discussed separately.

Upon completion of this period he was placed upon the following:

December 10. 6 A.M.: 1 glass of whole milk.

Breakfast: 1 piece of toast and butter; 1 apple or orange; 1 cup of chocolate (made with milk and sugar).

10 A.M.: 1 glass of milk.

Dinner: 1 bowl of strained vegetable soup; 2 glasses of milk; 1 serving of spinach.

4 P.M.: 1 glass of milk.

Supper: 1 piece of toast and butter; 1 glass of milk; 1 dish of unsweetened stewed peaches.

8 P.M.: 1 glass of milk.

[6] The eggs varied between 42 and 53 grams, but the correct weights were, of course, utilized in working up the dietary totals.

He was given the option at lunch of any one of the following instead of spinach: Lettuce, with oil and vinegar; parsnips, beets, cabbage, cauliflower, turnips, stewed celery, served without cream gravy.

December 17. Second glass of milk at supper was stopped and replaced with one slice of stale toast and butter.

December 20. Onions or tomatoes at lunch; ice-cream twice a week; stopped glass of milk at 6 A.M.; to breakfast added 1 soft-boiled egg.

December 27. Stopped milk at 4 P.M.; added a small piece of white meat of chicken at supper.

January 3, 1913. Stopped milk at 10 A.M. and 8 P.M.

January 8. Alternated small lamb chop with chicken at supper.

January 15. Alternated steak and fish at supper.

January 16. Small roasted potato at lunch.

January 17. Oysters at supper when desired.

January 19. Small amount of oatmeal and cream at breakfast and small amount of sugar added.

January 23. Small amount of rice at supper, with butter added.

February 1. Complete diet: Breakfast: Small amount of oatmeal and small amount each of sugar and cream. 1 apple or orange; 1 egg (boiled, fried, poached, or scrambled); 1 glass of milk; 1 piece of toast.

Dinner: 1 bowl of vegetable soup: 1 small roasted potato; 1 glass of milk or junket; 2 pieces of toast and butter; 1 serving of any of the following vegetables: spinach, lettuce, stewed celery, cabbage, beets, turnips, cauliflower, parsnips, onions, tomatoes. No flour or cream gravies. Ice-cream twice a week.

Supper: 1 glass of milk; 1 piece of toast and butter; 1 dish of unsweetened fruit (apricots, apples, prunes, or peaches); 1 helping of any of the following: White meat of chicken (small amount), small chop, small piece of steak, fish (small amount), one dozen oysters (raw or panned), 1 helping of rice and butter and salt.

The ward notes indicated his progress as follows:

December 11, 1912. Fingers were a little better, especially in the left hand. When asked to compare his condition with what it was when he first came to the hospital, he said, after a moment's thought, "I would say I am very much improved." Could walk around the yard. "Even the patients who sit on the porch remarked the improvement in walking." Helped the nurses do little things in the ward. Had had no medicine since admission except cascara for the last three days at bedtime.

December 19. Slight headache. Could bend his finger better and touched the thenar eminence for the first time with it.

December 27. Went home Christmas, and was pretty active, walking considerably for seven hours. Had some pain in his heels at bedtime. Went up stairs two steps at a time easily, but had

great pain in tendo Achillis on descending. He was kept in the hospital only to accustom him to exercise and greater range of food.

January 7, 1913. Hands were better than they had been since admission; he could open and flex them with great rapidity and ease. Day was warm, damp, and rainy, but he seemed to have

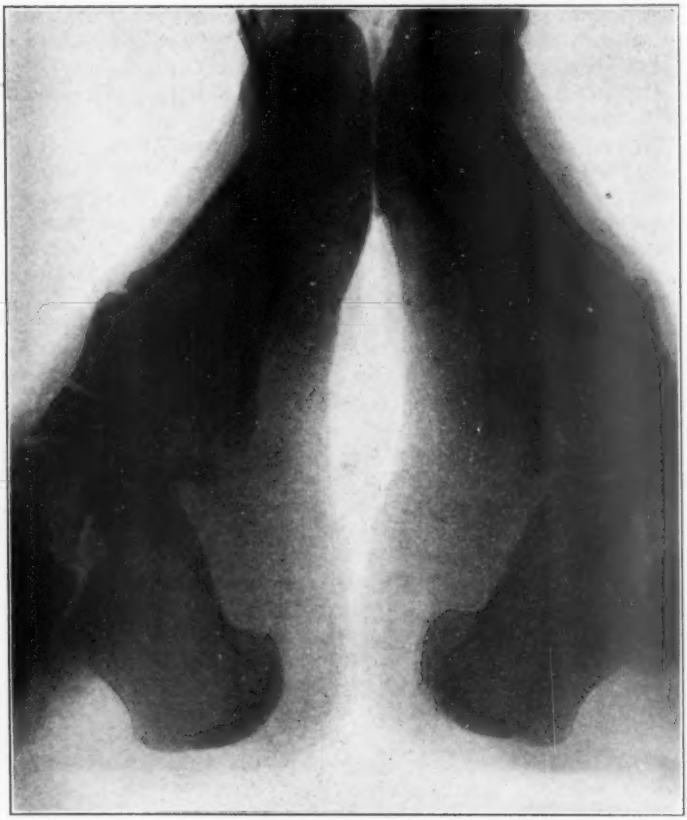

FIG. 1.—Feet of Case V. Notice erosion of left heel.

no particularly deleterious effects from it, as was usual when his joints were not so well.

January 27. Raw and rainy. Felt slight ache in muscles. Joints were all well. Went home the previous day and walked twenty-four squares. Milked three cows and was pleased at the full use of his hands. Weight 123½ pounds, which was more than for four months past and 6½ pounds more than on admission.

January 29. Hands, shoulders, limbs, etc., felt well. Had pain in both heels, especially the right, where there appeared to

be an exostosis posteriorly. The *x*-rays later showed this to be an osteoporosis, with a distinct hole in the bone.

February 11. Went skating in the park for one hour, also three days previously for one and three-fourths hours. Skated pretty hard. Heels steadily improving.

February 15. Discharged.

February 28. The patient returned for observation, and was in excellent shape.

He was sent for on June 11, 1913, and said that he was as well as before he was affected with arthritis. Sometimes at night after working all day he felt a slight soreness in the heel, but this was decreasing. and was felt only occasionally. Two days before, on June 9, he had piled up in the field about two and one-half tons of bales of rye, which indicates freedom of movement in joints and muscles. His weight was 124¼ pounds, 4 pounds less than when in the ward. This loss was probably owing largely to his hard work, but also to a fall from a horse, in which he injured his wrist. He was nauseated and shocked, and for some days was "off his feed," following the accident. It will be noted that colonic lavage and buttermilk were omitted entirely in this case. This point will be discussed later. On October 4, when seen, he was actively engaged in teaching, and was very happy in his present condition of health.

CASE VI.—Mrs. H. L., aged about fifty-eight years. Admitted to the hospital on December 31, 1912. Referred by Dr. Francis O. Allen. The patient had excellent health until the onset of the present trouble, four years previously. It began in the ankles and progressed to the arms, hips, hands, and wrists, the latter two becoming involved chiefly during the past year. Physical examination revealed myocarditis, a slight systolic apical murmur, and some cardiac hypertrophy, with a blood pressure of 202 systolic and 110 diastolic. There was distinct though no great swelling on the dorsum of each hand and wrist and over some of the knuckles.

She complained of tenderness on pressure at these sites, and of pain upon motion of arms or legs, making all activities a burden and an effort. Appetite, sleep, and bowels were undisturbed. Her weight was 151¾ pounds. Her blood and urine were essentially normal, and the latter was at all times free from indican. She had no fever. The *x*-ray examination revealed both stomach and large bowel to be greatly elongated and ptosed. The bowel was tortuous, especially at the splenic flexure where it crossed the stomach and divided the latter in half. The joints and bones of both hands and wrists showed both atrophic and hypertrophic changes, with some inflammatory involvement.

Treatment was instituted on January 4, 1913, with daily colonic lavage and the following dietary:

Breakfast: 1 apple, 1 egg, 1 piece of toast, and 1 piece of butter.

Dinner: 1 bowl of broth, stewed tomatoes, and an apple baked

without sugar. In place of tomatoes she was given an option of spinach, celery, parsnips, or turnips.

Supper: 1 egg, 1 slice of toast and butter, 1 helping of stewed fruit (made without sugar), and 1 glass of milk.

This yielded about 1000 calories or about 7 calories per pound of body weight or 15 calories per kilo. This diet was changed as follows on the days indicated:

January 10. Lettuce, with small amount of French dressing, at supper; celery stalks once daily.

January 14. 1 glass of milk at breakfast.

January 21. Stopped glass of milk at supper and substituted one small roasted potato.

January 22. Gave small piece of chicken at supper.

January 23. Celery at lunch instead of supper. Alternated with chicken, a small chop, or small amount of beefsteak or fish.

January 27. Stopped 1 glass of milk at breakfast and gave 1 slice of toast additional.

February 3. Gave a total of two green vegetables at lunch.

February 12. Gave stewed fruits made with sugar.

February 16. Small dish of oatmeal and cream at breakfast, and stopped 1 slice of toast.

February 17. Gave colonic irrigations every other day instead of daily.

February 19. Small amount ice-cream thrice weekly instead of stewed fruit at lunch.

February 27. 1 apple at bedtime; 6 panned oysters at lunch daily.

February 28. Beans or peas instead of potato at supper optionally.

March 7. Meals averaged as follows:

Breakfast: 1 medium-sized apple; 2 tablespoonfuls of oatmeal; 1½ ounces of cream; 1 poached egg; 1 piece of toast; 1 piece of butter (6½ grams); 1 cup of coffee (f℥ij coffee, f℥ij cream, 1 cup of hot water; she preferred no sugar).[7]

Lunch or Dinner: f℥ix of clear soup; 6 panned oysters; 2 tablespoonfuls of spinach; 2 tablespoonfuls of stewed tomatoes; 2 stalks of celery; 6 stewed figs and 1 tablespoonful of juice.

Supper: 2 pieces of toast; 1 piece of butter, 6½ gram; 2 tablespoonfuls of beans; 2 broiled lamb chops (small); 1 dish of lettuce and 1 tablespoonful of mayonnaise dressing; 2 tablespoonfuls of apple sauce.

Her progress, as indicated by almost daily notes made at the time, follows:

Diet begun January 4, P.M.

January 5. No change, except that hand was slightly more sore, possibly because of the rather raw day.

[7] The liquid measurements are often given in drams and ounces as this was more convenient for the nurses. The food weights are always in grams.

January 6. No definite change. Possibly less pain in metatarsophalangeal joint of left little finger and also possibly slightly less swelling. She had pain the previous night.

January 7. Pain in the left hand was less on pressure. The right hand was about as the day before. The shoulders hurt less during the night, and were better this date.

January 9. Patient said she felt "very spry." Hands were distinctly less tender to touch and seemed reduced in size. The skin over them was more wrinkled, and she had had but little pain in shoulders and none elsewhere. Knees did not hurt at all.

January 16. Patient said she was surprised to notice rain in the night, as her joints had failed to forewarn her of it for practically the first time in six months. Hands improving and she felt well. No ache in the arms.

January 25. Slightly more pain on pressure over the wrist sore points. Was slightly "conscious of her bones" during the night.

February 5. Walked nine squares in the morning. Wrists were better than they had been to date. Slight stiffness in the middle finger of left hand and little finger of the right hand.

February 23. Patient noticed that she had caught a "cold," with sore throat, malaise, fever, aching in bones with headache and stiff neck the two previous days. Felt better. Bowels had been well moved. Joints *per se* were no worse than the rest of her bones (which ached) during the attack. In bed two days.

February 25. Up and out. Felt a little "weak," but joints were all right. Given quinine, gr. ij, t. i. d.

March 4. Received more than she wanted to eat. Pain difficult to find on pressure, and the patient was really entirely well. Had been kept in the hospital only to instruct her "how to live." Quinine was discontinued.

March 8. Discharged from hospital. Weight, 150½ pounds.

The subsequent course of this patient was that upon getting home she took liberties with her diet within the first twenty-four hours, having had among other things a "charlotte russe." She appeared at once for treatment because of slight sensitiveness in the arms. After leaving the hospital she lived under unfavorable conditions, occasionally skipping a meal or substituting things other than those ordered. It was found nearly impossible in this case to insure the patient's getting the exact dietary prescribed, though she adhered to it in the main, and kept in fair shape, leaving for the South on May 12, weighing 142¾ pounds. At this time the only evidences of her trouble were some tenderness on pressure over the sore spots on the wrists and a slight premonition in the shafts of her arms of a "change of weather." She felt active and in excellent health, and was urged to be more careful in her diet. Advice by letter from her home in the South on August 7 reported her entirely free from pain anywhere and feeling perfectly well.

(To be continued.)

REVIEWS

MEDICAL MEN AND THE LAW. A MODERN TREATISE ON THE LEGAL RIGHTS, DUTIES, AND LIABILITIES OF PHYSICIANS AND SURGEONS. By HUGH EMMETT CULBERTSON, ESQ., member of the Ohio and New York Bars; Contributing Editor to many legal publications. Pp. 325. Philadelphia and New York: Lea & Febiger, 1913.

THIS work represents an effort on the part of the author as set forth in the preface to present the main features in modern law as it pertains to physicians and surgeons. The need for such a work is manifested in the utter lack of knowledge of the law as it bears upon medical matters shown by the average practitioner and his consequent inability to properly discharge many of the duties arising from his position as an advisor either to his patients or the community.

The author has combined the main points wherein medicine and law touch each other, based on actual court decisions. The discussions deal with every possible phase of medical law and are expressed in an unusually clear, concise, and interesting manner. Each chapter represents more or less a dissertation on one particular phase of this subject. The questions of qualifications for practice, compensation, malpractice, criminal liability, physicians and surgeons as witnesses, and wills are the titles of some of the especially interesting chapters. The table of contents and index make reference to any subject simple and easy. As a reference book for physicians or as a compend for lawyers the book should have a high place. The book is well printed on heavy paper and contains very few typographical errors. F. H. K.

OBSTETRICS. By W. P. MANTON, M.D., formerly Professor of Obstetrics and Clinical Gynecology, Detroit College of Medicine; Gynecologist to the Harper Hospital. Second Edition; Pp. 292; 97 illustrations. Philadelphia and New York: Lea & Febiger, 1913.

THAT this little book has attained its purpose is evidenced by the appearance of a second edition. While such a manual is in-

tended primarily for the student, the author has so carefully revised the book that it should prove helpful to the practitioner as well. Although limitations of space have forced the curtailment of some subjects, yet the important fundamentals have been well presented. Appended to each chapter is found a list of pertinent questions as an aid to the student in rapid review work. The principles stated governing the management of pregnancy, the conduct of labor, and the choice and technique of operative procedures are in accord with the best modern ideas. The recommendation of atropine in doses of $\frac{1}{10}$ grain in the treatment of salivation as mentioned on page 69 is no doubt due to a typographical error. The illustrations are well chosen. The book should continue to find favor among those who wish a small, accurate manual of obstetrics suitable for quick reference work. P. F. W.

THE PRINCIPLES AND PRACTICE OF GYNECOLOGY. FOR STUDENTS AND PRACTIONERS. By E. C. DUDLEY, A.M., M.D., Professor of Gynecology, Northwestern University Medical School; Gynecologist to St. Luke's Hospital, Chicago. Sixth edition. Pp. 795; 439 illustrations and 24 full-page plates in colors and monochrome. Philadelphia and New York: Lea & Febinger, 1913.

RECOGNIZED as an authority on the subject since its initial appearance fifteen years ago, Dudley's Gynecology presents in the sixth edition a thoroughly modern text-book embodying all the recent advances in gynecology. In this edition the text has been subjected to a careful revision, thus allowing the introduction of much new material without increasing the size of the volume. The book possesses a wealth of original and accurately executed illustrations, certain series of which serve to portray step by step the various stages of different operative procedures, twenty-five drawings and diagrams being used to explain the operation of perineorrhaphy.

The classification of the subject matter follows that of previous editions. Thus instead of all the pathological conditions of an organ being included under such a heading we find the infections and inflammations of the pelvic organs following one another in the manner of their etiological and pathological sequence. The first part of the book devoted to the general principles concludes with a chapter on the relation of dress to the diseases of women, discussing briefly the perversion of pelvic physiology by the present-day manner of dress and living. The author defines clearly the uses and the limitations of local therapy and cautions especially against the improper and often unsuitable use of intra-uterine medication. His personal experience is expressed in the preference for the expectant and palliative, rather than the surgical treatment, curettage, in acute metritis.

Mention is always made of *x*-ray therapy in those conditions amenable to its influence, but it may not yet be accepted as a substitute for operative measures in myoma. The use of the *x*-rays and of radium is to be restricted to the palliative treatment of inoperable or carefully selected cases of myoma and other tumor formations. Beside the operations personally preferred by the author in the treatment of displacements of the uterus, other well known methods are fully described and illustrated. Worthy of note is the inclusion of the highly favorable results obtained in another clinic with the operation devised by the author for the relief of pathological anteflexion of the uterus, and its accompanying dysmenorrhea and sterility. In the chapter on diagnosis and treatment of bladder lesions some cystoscopes more recent than those described might have been mentioned. The final section on disorders of menstruation and sterility closes with a chapter discussing an original plastic operation for the treatment of incontinence of urine.

The book is a splendid exposition of gynecologic, especially plastic, surgery, and this edition fully maintains the eminence established by its predecessors. P. F. W.

"The Brain and Spinal Cord." A Manual for the Study of the Morphology and Fibre Tracts of the Central Nervous System. By Dr. Emil Villiger. Translated by George A. Piersol, M.D., Sc.D. Philadelphia and London: J. B. Lippincott Co.

There are many excellent works on the brain and spinal cord in the German and French languages, but really adequate expositions of the subject in the English language are rare.

The selection of Villiger's work for translation was wise and timely. In the original it lacked the encyclopedic character found in other well-known anatomies, thereby gaining as a text-book.

The work is divided into three parts: Part I.—Morphology; Part II—Fibre-tracts; Part III—Serial Sections of the Brain Stem.

Ninety-three pages are devoted to the first part in which the student is never allowed to lose sight of the embryology of the cerebrospinal axis. The illustrations are numerous and for the most part excellent. The section dealing with the cerebellum (pp. 72 to 77) is illustrated with figures possibly more diagrammatic than accurate. For instance, the relation of the pyramid to the lobus biventer is hardly borne out in the human brain. In the text (p. 75) one finds the following regarding the secondary flocculus: "Lateral to the latter, between the lobulus quadrangularis of the

superior lobes and the lobulus biventer is seen the accessory flocculus, flocculus secundaris." That the parafloccular mass is sometimes found in the human subject in a very rudimentary condition is possibly true, but careful search will often fail to discover what is so well marked in some of the lower animals.

In the second part the first six pages are devoted to the methods of studying the fibre-tracts. This also is wisely flavored with the embryological point of view. The illustrations of Part II are beautifully clear and the text critical and excellent. For instance, the subject of taste-conduction is dealt with in the following manner: the several theories are lucidly stated, the last to be given (chorda, geniculate, intermedius, medulla) being introduced by "Finally, according to the view which seems, perhaps, the most reasonable," etc. This careful conservatism is the key-note of the book.

The third and last section presenting sections of the brain stem from the anterior end of the corpus callosum to the quadrigeminal region; from the caudal end of the medulla oblongata to the quadrigeminal region and one sagittal plane leaves nothing to be desired in accuracy and definition.

The whole work is a credit to the author, translator, and publisher, and can not fail to excite the enthusiasm of the student.

A. R. A.

A Clinical Manual of Mental Diseases. By Francis X. Dercum, M.D., Ph.D., Professor of Nervous and Mental Diseases, Jefferson Medical College, Philadelphia. Pp. 425. Philadelphia and London: W. B. Saunders Co., 1913.

There is no one who is better qualified to write a practical book on insanity than Dr. Dercum, for he has had a large experience with insane patients and has taught medicine for years. There is indeed a need for a short practical book such as this, for the student has little time to read a larger work, and the average practitioner even less. To them it is a question, is this man insane or not, and how can I recognize that he is insane? At the present time there is a widespread tendency to abandon the older classifications and conceptions of insanity. This is due largely to the work of Freud, Bleuler, Jung and their followers. Whether one believes in their teaching or not, and Dr. Dercum does not, it would be folly to attempt to teach their theories to the average medical student.

The subject matter is well arranged and presented in a logical and comprehensive manner. It is eminently a book for students and medical practitioners, and can be highly recommended.

T. H. W.

GLYCOSURIA AND DIABETES. By FREDERICK M. ALLEN, A.B. M.D. Boston: W. M. Leonard, 1913.

THIS remarkable book of nearly 1200 pages, combines an excellent presentation of the literature of diabetes and the results of experimental work on 200 dogs, 200 cats, and a smaller number of rabbits and guinea-pigs. The style of the writing is clear and, for the most part, absolutely convincing. If the experimental work is confirmed, the book will rank as a classic on the subject. No one interested in diabetes as a scientific problem can afford to be without this volume.

Allen's investigations were along two lines: (1) The behavior of sugars in the body, and (2) the production and modification of diabetes.

The various methods to determine sugar tolerance were first tested and preference was given to that of subcutaneous injection. In the normal animal the subcutaneous tolerance of levulose was a small fraction of that of dextrose. It was found that neither diabetes nor its complications could be produced in normal or predisposed animals by prolonged excess of dextrose. The "paradoxical law" is thus enunciated; the more sugar given, the more utilized. All types of non-diabetic animals follow this law and it holds true with alimentary, hunger, toxic, phlorhizin, adrenalin, thyroid, and nervous glycosurias. Hence, these are not diabetic conditions, for there is a true limit of tolerance in the diabetic organism. Furthermore, if the common sugars are given orally to normal animals, they have an antidiuretic effect and the same effect is produced when sugar is given in the above named glycosurias. The administered sugar acts as if it were in colloid combination in the blood. But if sugar be given to the truly diabetic, diuresis at once sets in, the sugar behaving like a crystalloid. This test proves that diabetes cannot be due to an overproduction of sugar.

As regards the second experimental portion of the book, the author distinguishes between diabetes gravis, which follows uncomplicated removal of nine-tenths of the pancreas and in which dextrose is excreted on a meat diet, and diabetes levis, in which a seventh or an eighth of the pancreas remains in position and dextrose is excreted on a starchy but not on a meat diet. When a sixth of the pancreas is left, a transient diabetes may ensue but never a permanent one. After establishing these facts experimentally, dogs were prepared which were not diabetic nor yet could develop diabetes in the ordinary course of events, but which had so little surplus of pancreatic tissue that untoward influences might render them diabetic. In this condition the following influences proved to be negative factors so far as inducing diabetes was concerned; alimentary glycosuria, acid intoxication, toxic glycosurias,

phlorhizin glycosuria, excess of epinephrin or thyroid administration as well as operative reduction of adrenal or thyroid tissue or both, and certain nervous and circulatory alterations. These experiments strike a hard blow at the polyglandular doctrine of von Noorden and his pupils, and show it to be out of harmony with the facts. The only influences found which induced permanent diabetes in the predisposed dogs were: (1) Bernard's puncture which was followed by the characteristic changes in the islands of Langerhans; and (2) a disturbance in the blood supply to the pancreas which occurred after rapid obliteration of the portal vein. It was found that ligation of the pancreatic ducts in dogs with pancreas remnants, tended to the preservation of the islands of Langerhans and the advisability of the enervation of the pancreas remnant is also suggested in order to remove the nervous effects. In the author's mind the sequence of causation of human diabetes is to be expressed as follows: Nervous disorder, impaired function of the islands of Langerhans, deficiency of the pancreatic amboceptor, glycosuria, and other symptoms.

This book, the work of a hitherto unknown author, is a credit to American medical science and to the Harvard Medical School, in which it was accomplished. G. L.

DISEASES OF THE STOMACH, INTESTINES, AND PANCREAS. By ROBERT COLEMAN KEMP, M.D., Professor of Gastro-intestinal Diseases in the New York School of Clinical Medicine. Second Edition. Pp. 1021; 388 illustrations. Philadelphia and London: W. B. Saunders Company, 1912.

THE first edition of this text-book was favorably reviewed in this JOURNAL in 1911 (N. S., cxlii, 892). It was suggested at that time (not by the present reviewer, however) that the book might well include a consideration of diseases of the liver and pancreas. In the new edition the author has followed this suggestion so far as the latter organ is concerned and has devoted a little over 100 pages to the subject. He has also devoted a chapter to infections by the Bacillus coli and has rewritten the article on duodenal ulcer in accordance with the views of recent authorities on the subject. The chapter on Methods of Diagnosis in pancreatic disease contains a rather full account of the numerous tests that have been suggested. Fortunately for the general practitioner the author emphasizes a very few methods which he considers of value: the examination of the motor and secretory functions of the stomach, the general test of the intestinal functions by the Schmidt-Strassburger diet, the Boldyreff (or Volhard) method of securing the pancreatic juice, the examination of the urine for sugar, the fecal

findings after the administration of pancreatic extract and the examination of the blood for the rapidity of clotting. This volume covers its wide field with fidelity and for the most part sound judgment. It should be of use for reference particularly for those who do not have access to original articles and monographs. As stated in the previous review the references are more scanty than one would wish but this is a fault common to most American (and English) medical books and is probably to be laid at the door of the publishers and purchasing public rather than to the particular author concerned. C. B. F.

A Text-book on the Pathogenic Bacteria and Protozoa. For Students and Physicians. By Joseph McFarland, M.D., Professor of Pathology and Bacteriology in the Medico-Chirurgical College of Philadelphia, etc. Seventh Edition. Pp. 878; 293 illustrations. Philadelphia and London: W. B. Saunders & Co., 1912.

Dr. McFarland's previous editions of this book were confined to bacteria but the growth of microbiology and the demands of friends of the book as well as of teaching, required an enlargement to include the pathogenic protozoa. The author lays out for himself in the preface the tasks of describing all the animal and vegetable microörganisms of pathogenic importance, with their mode of action, the tests necessary to show their presence, and the important techniques now in use. The treatment of the last is particularly succinct. In the various chapters upon the individual microbes, definition, habitat, morphology, and cultural characters are sufficiently covered but most attention is given to toxicity, pathogenesis, lesions, immunity, and treatment depending upon the last. Many references are given and all authors are treated with full consideration. The bibliographical list before the index is serviceable. The illustrations are excellent and each one means something. Dr. McFarland's style is, as usual, exact and pointed but fluently readable withal. The diseases due to the filterable viruses are nowadays considered with the infectious ones. A chapter on this subject is missing but the omission is not inconsistent with the task the author has assumed and fulfilled. It is to be hoped that it will be convenient to include this subject in future editions. The book in its present form is a welcome one and will be popular.
H. F.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

CHIEF OF THE DEPARTMENT OF INTERNAL MEDICINE, CLIFTON SPRINGS SANATORIUM AND HOSPITAL, CLIFTON SPRINGS, NEW YORK.

The Etiology of Relapse in Malarial Infections.—JAMES (*Jour. Infect. Dis.*, 1913, xii, 277) believes the asexual cycle alone is the cause of relapse in malaria. That the asexual cycle often persists in so-called spontaneous cures can be proved in numbers by finding the parasites by the thick film method. Infections insufficiently treated with small doses of quinine will relapse because the parasites of the asexual cycle in the spleen and bone marrow are little if at all affected. Early vigorous treatment is indicated, as the older the asexual cycle the more resistant to quinine it becomes. If parasites persist in the blood during treatment, faulty absorption of the drug is sure to exist, and the method of administration should be changed. It is easier to eradicate the infection in patients in good health because of the aid of the natural protective forces of the body. The practical importance lies in the guide to treatment. Among Americans in the Canal Zone, when liquid sulphate of quinine was given in doses of 20 grains a day by mouth, recurrent cases followed in large numbers at short intervals. For several years it was increased to 20 grains on diagnosis, and 10 grains three times a day for at least ten days. The number of recurrent cases was noticeably diminished, among the Americans but not sufficiently among the poorly nourished Europeans. A treatment was then instituted of 45 grains a day. This has practically eradicated malaria among the Americans, and to a large extent among the European laborers. The latter, however, treat mild infections themselves with small doses and so produce a relatively quinine-immune asexual cycle that is more difficult to eradicate. To stamp out the disease this vigorous, early treatment to prevent relapses is one of the most powerful weapons.

An Outbreak of Septic Sore Throat.—MANN (*Jour. Infect. Dis.*, 1913, xii, 481), in studying most completely an epidemic of septic sore throat in Concord, N. H., has convicted the milk supply again, as was the case in the Chicago, Baltimore, and Boston outbreaks. A streptococcus was the cause and tonsillitis with marked cervical adenitis the principal features. More adults were affected, however, than children. Mann emphasizes cream also as a great source of danger. It was clear that the milk was infected through handling by individuals suffering with the disease, and the cream when separated retained the infected organisms. He believes the standard of intelligence among dairymen is too low. The public should demand that the producers be able to recognize the importance of safe-guarding milk against bacterial contamination. It is just as important to safeguard the cream supply. Under present standards it is not safe to use market milk in the raw state.

Meiostagmin and Epiphamin Reactions in the Diagnosis of Carcinoma.—BURMEISTER (*Jour. Infect. Dis.*, 1913, xii, 458) has applied Ascoli's meiostagmin reaction to the diagnosis of carcinoma. Considering the successful application by Ascoli and coworkers, and the few reports in this country, Burmeister's conclusions are especially interesting. He finds that a decidedly negative meiostagmin reaction is of more value than a positive one, and may be considered of some weight in ruling out carcinoma. A moderately or even strongly positive reaction is not necessarily indicative of malignant tumor. The epiphamin reaction is valueless in the diagnosis of malignant tumors. The results obtained by other workers who have employed the method in the diagnosis of conditions other than carcinoma are explained by the range of error. In no single instance were two like curves obtained by the same method for the same serum and antigen mixtures, even with distilled waters instead of antigen and antiserum the extremes of the range of error were too great for practical purposes.

Droplet Infection in Diphtheria.—FLÜGGE and his pupils have emphasized the importance of droplet infection in the spread of tubercle bacilli, but there has been no experimental work with reference to the emission of diphtheria bacilli. TEAGUE (*Jour. Infect. Dis.*, 1913, xii, 398) has obtained very interesting results in this regard. He exposed blood-serum-glucose plates about three inches from the mouths of diphtheria patients during coughing, singing, counting, and talking. Of 51 cases, 65 per cent. emitted viable diphtheria bacilli. The plates indicated that droplets containing viable diphtheria bacilli are emitted frequently by diphtheria patients in talking and coughing, but usually in small numbers. To prove that laryngeal cases emit vastly more droplets containing bacilli than pharyngeal and tonsillar cases, Teague's larynx, pharynx, and mouth were swabbed with B. prodigiosus at different times, and plates exposed during coughing. But results showed no more droplets thrown out from the larynx than from the mouth. B. prodigiosus in droplets have been borne in the air 53 meters along a corridor and up two flights of stairs, and even 600 meters on the breeze. Since B. diphtheriæ is much more resistant to drying, Teague assumes it would be carried even greater distances.

SURGERY

UNDER THE CHARGE OF

J. WILLIAM WHITE, M.D.,

FORMERLY JOHN RHEA BARTON PROFESSOR OF SURGERY IN THE UNIVERSITY OF PENNSYLVANIA AND SURGEON TO THE UNIVERSITY HOSPITAL,

AND

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL HOSPITAL, AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

Anesthesia of the Brachial Plexus.—KULENKAMPFF (*Zentralbl. f. Chir.*, 1913, xl, 849) wishes to explain the disturbances which have been reported in connection with his method of anesthetizing the brachial plexus by injection with local anesthetic solutions. He has employed the method in over 200 cases, but has not met with the accidents reported. He admits that the patients complain, occasionally, of distress in the chest but not in the arm. In the introduction of the needle, as soon as it is turned backward and medialward, it is close to the plexus and usually produces paresthesia. He believes that this is due to an irritation of the first intercostal nerve which is chiefly concerned in the formation of the ulnar nerve. The needle may cause disturbance by perforation of the pleura, an accident which has been reported several times. Kulenkampff reviews the literature briefly in regard to the character of the disturbances reported and the various interpretations for them. He concludes that in all cases the disturbances were similar and accounts for them by an irritation of the pleura or of the first intercostal nerve. He has long been familiar with the same clinical picture, not in connection with anesthetization of the brachial plexus, but with the performance of paravertebral injection anesthesia. He has seen it in connection with thoracotomy, kidney operations, and transpleural drainage of subphrenic abscess. There is a brief and characteristic free interval between the first pricking sensation from the penetration of the nerve by the needle point and the later severe pain, which finally disappears. The second severe pain is regarded as reflex. Similar reflex effects have been observed in connection with the peritoneum, but more particularly with the pleura. Death has occurred from puncture of the pleura. With regard to the cases reported in which paralysis of the phrenic was supposed to have resulted from injection of the brachial plexus, Kulenkampff says that the evidence is lacking to show that the phrenic is particularly sensitive and possesses sensory fibers. He regards it as significant that the diaphragm has been divided painlessly without anesthetization of the phrenic nerve, if the intercostal nerves have first been anesthetized. This he has demonstrated himself in dividing the diaphragm in transpleural drainage of a subphrenic abscess. He believes that the disturbances reported were not due to a paralysis as maintained by several writers, but to either a pleural wound or a pricking of the first intercostal nerve.

A Study of the Pathological Anatomy and Physiology of Amyloid Degeneration of the Kidneys in the Tuberculous.—Leon-Kinberg (*Journ. D'Urolog.*, 1913, iii, 561) says that in the course of a chronic pulmonary tuberculosis, amyloid degeneration attacks the liver, spleen, and suprarenal capsules before attacking the kidneys. It is not rare to encounter in others massive amyloid disease, while in the kidneys only loops of the glomeruli or arteries of the pyramids are infiltrated with amyloid substance. At this period, except in cases with a preëxisting chronic renal lesion, there are in general no clinical symptoms of nephritis. Only albuminuria or at times an abnormal polyuria can attract attention to it. A study of the urinary secretion in these cases permits one to recognize an important syndrome. The percentage of urea is always very low, that of the chlorides below the normal. Yet the secretion of the chlorides and even that of the urea is sufficient. These signs are an evidence of an exaggeration of the power of concentration of the kidney, a kind of hypersecretion. When the histological examinations can be made under good conditions, there is found a particular hypertrophy of the cells of the cortical tubes, which seem to be the histological translation of hypersecretion. From the practical point of view it is believed that the establishment in a tuberculous patient of the urological syndrome described will often permit the diagnosis of amyloid degeneration to be made early, before the appearance of great edema, massive albuminuria, and uncorrectable diarrhea.

Thirteen Cases of Traumatic Rupture of the Spleen without External Wound.—Norlein (*Archiv. geb. d. Chir.*, 1913, vii, 520) from his study of the 13 cases which he reports and of the literature, says that the number of ruptures of the spleen that are brought to the hospital early enough to have some chance from a surgical operation, appear to increase rapidly. All surgeons should, therefore, be well informed concerning the etiology of the lesions associated, their symptoms, and their treatment. Although we lack pathognomonic signs of rupture of the spleen, it is nevertheless possible to make a probable diagnosis in the majority of cases. The best treatment is to make a median exploratory laparotomy incision, from which a transverse incision to the left is carried across the rectus, to expose and treat the rupture. Whenever possible, one should respect the integrity of the spleen. What is needed now in splenic surgery is the perfection of conservative methods and especially methods of suture.

An Instance of a Large Ureteral Calculus and Some Other Cases of Calculi.—Wherry (*Brit. Med. Journ.*, May 17, 1913, 1043) reports an interesting case in which two large ureteral calculi were removed through the peritoneal cavity, with success. The patient was a girl, aged sixteen years, in whose condition there was little to call attention to her real malady. She had on admission, joint and epigastric pains swelling of the knee-joints on both sides and pain in the right side of the chest. The urine was acid, free of albumin and sugar. She was watched during five weeks until an access of fever and abdominal pain led to further examination of her urine, in which some pus and blood were found, and some crystals of oxalic acid. Digital examin-

ation of the rectum disclosed a large mass to the right of the uterus and the *x*-rays made it almost certain that there were calculi in the ureter. Through a median incision the abdomen was opened, and then with the patient in the Trendelenburg position two large calculi were found in the pelvic portion of the ureter. The stones were fixed and could not be pushed upward or downward. The ureter was clamped above, an incision was made, and the stones removed; about two ounces of purulent urine were swabbed out. The ureter was sewn up with catgut, using a harelip needle. The patient was then placed in the horizontal position and the suturing tested, so that the pressure in the ureters was tested in two positions. The clamp was removed and the abdomen closed in the usual way without the use of drainage. A good recovery was made, the temperature came down at once, and except for washing out the bladder with boric solution there was no trouble with the nursing. Together the stones measured $2\frac{1}{8}$ inches by 1 inch in diameter, and their weight when dry was 226 grains and 91 grains, or a total of 317 grains.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

PROFESSOR OF APPLIED THERAPEUTICS IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

Digitalis and Strophanthin Therapy.—SCHENK (*Wein. klin. Rundschau.*, 1913, xxvii, 375) recommends digistrophan which is a combination of digitalis and strophanthin for the treatment of disturbances of compensation in heart disease. Digistrophan has the advantage of combining the tonic action of digitalis with the regulating action of strophanthin in cases of failure of the cardiac muscle. Schenk claims that digistrophan is prompt in its action, certain in its effects, and stabile in its composition. He says that the remedy is easy to take, has no untoward effects, and deserves a wide use.

Three cases of Amebic Dysentery Treated with Salvarsan.—MADHAUS and HILL (*Jour. Amer. Med. Assoc.*, 1913, lxi, 385) report three cases of amebic dysentery in detail that were apparently cured by salvarsan. One of these patients had a positive Wassermann reaction and after receiving neosalvarsan together with mixed treatment the bowel movements became normal with no blood or mucus present, and no amebæ. In this patient there was no evidence of syphilis except possibly the fact that before the treatment the man was bald and since has developed an excellent growth of hair. The two remaining cases had negative Wassermann reactions and no clinical evidence of syphilis. They had contracted in the Philippines amebic dysentery which recurred frequently until it became practically a chronic con-

dition with acute exacerbations. Following the salvarsan treatment, a marked and prompt improvement occurred and in a comparatively short time the amebæ together with the mucus and blood disappeared from the stools. Madhaus and Hill say that it is perfectly evident that these three cases prove nothing, but the results have been so striking that it has seemed desirable to them to report these cases in order that others with more clinical material may investigate the matter further.

The Intravenous Injections of Small Amounts of Human Blood for the Treatment of Severe Anemias.—WEBER (*Münch. Med. Woch.*, 1913, xl, 1307) suggests the intravenous injection of 5 c.c. of defibrinated human blood for the treatment of cases of severe anemias. The blood is obtained from a healthy donor from six to twenty-four hours before use. He has made forty-six such injections with only very slight reactions following the injection. Weber avoids by these small injections the toxic effects that frequently follow larger amounts, and the therapeutic results have been very good. The technique is much simpler than that for direct transfusion and it seems that the beneficial effects are due not so much to the amount of blood injected as to a stimulating action on the blood forming organs. This treatment should be combined with proper dietetic and hygienic measures and supplemented by arsenic to secure the best results.

One Thousand Subcutaneous Injections of Neosalvarsan.—WECHSELMANN (*Münch. Med. Woch.*, 1913, lx, 1309) writes concerning the subcutaneous use of neosalvarsan. He has given the remedy in this way lately with great success. The technique is described in detail. The injection is given into the area around the great trochanter and great care should be taken that the needle is free and the injection delivered directly over the fascia. The injection must not be made into the fascia, muscle, or subcutaneous fat. This method, while technically more difficult than intravenous or intramuscular injection has, according to Weschselmann, many advantages. There are no untoward by-effects that follow the administration of salvarsan in this way, and it is possible to keep a patient more continuously under the influence of the remedy. If the injection is properly done necrosis does not occur and no more pain results than that which follows intramuscular injections of mercury. Wechselmann gives the remedy in concentrated solution giving from 0.5 to 0.9 gm. of neosalvarsan dissolved in 1 c.c. of freshly distilled sterile salt solution. Neosalvarsan, because of its neutral reaction and non-irritating properties may be given in this way without producing inflammation or necrosis. The remedy is readily absorbed; 75 to 85 per cent. being absorbed in one week, and after six weeks only about 5 per cent. remains unabsorbed.

Amino-acids and Sugar in Rectal Feeding.—SHORT AND BYWATERS (*Brit. Med. Jour.*, 1913, 2739, 1361) review the literature on the subject of rectal feeding and relate their own observations on the absorption of food when introduced in the form of nutrient enemas. They determined the urinary output of total nitrogen and ammonia during periods of fasting followed by periods of rectal feeding. Short

and Bywaters say that the older observations on the absorption of foodstuffs from rectal enemas based on the analysis of rectal "wash outs" are unreliable. The daily output of nitrogen in the urine of patients given nutrient enemas of milk or eggs peptonized for 20 to 30 minutes demonstrates that almost no nitrogenous matter is absorbed. Modern physiological opinion holds that proteins are absorbed principally as amino-acids. The failure of the rectum to absorb ordinary nutrient enemas is largely due to the fact that peptones are given instead of amino-acids. Chemically prepared amino-acids or milk pancreatinized for twenty-four hours so that amino-acids are separated, allows of a much better absorption of nitrogenous foodstuffs from the rectum as demonstrated in five cases by the high nitrogen output in the urine. The low output of ammonia nitrogen shows that the high output was not due to the absorption of putrefactive bodies. The rectal washings were not offensive. Dextrose is much better absorbed than lactose and relieves the acidosis due to starvation. Fat is not well absorbed. Scarcely any of the fat of ordinary milk enemas is retained. The best nutrient enema consists of milk pancreatinized for twenty-four hours, with the addition of 5 per cent. pure dextrose. They consider that the best form of nutrient enema should be prepared as follows: To a pint and a half of milk, boiled and cooled add one half an ounce of some reliable pancreatic fluid or four pancreatic tablets. Keep in the incubator twenty-four hours. Add one half an ounce of pure dextrose. Give five ounces every four hours, or, if the patient can retain it, ten ounces every eight hours.

PEDIATRICS

UNDER THE CHARGE OF

LOUIS STARR, M.D., AND THOMPSON S. WESTCOTT, M.D.,

OF PHILADELPHIA.

The Diagnosis and Treatment of Acute Mastoiditis.—GEORGE H. MATHEWSON (*Canadian Med. Assoc. Jour.*, 1913, iii, 672), puts into concrete form the current teachings on this subject. Acute mastoiditis resulting from, or accompanying middle ear disease is the form commonly seen, and as it can often be aborted in its incipient stage its early diagnosis is of vital importance. The presence of an acute or subacute otitis media is almost essential to the development and diagnosis of an acute mastoiditis. The symptoms of acute mastoiditis are tenderness on pressure over the mastoid process, pain in that region, edema and redness of the soft parts behind the auricle, in some cases abscess, prolapse of the posterior superior wall of the membranous meatus near the drum membrane, excessive, creamy, purulent discharge, and elevation of temperature. The most important symptom is tenderness over the mastoid process, especially just behind the external meatus, at the tip of the process, and less frequently about an inch

behind the first point mentioned. Pain in the mastoid is not constant. Edema of the soft parts is frequent but is a late symptom. Furunculosis of the meatus quite as often causes edema here and may simulate mastoid tenderness if the meatus is pulled on while pressure is made over the mastoid. Prolapse of the postero-superior wall of the meatus if present is an indication for operation. If the purulent discharge is great it indicates mastoid involvement. Elevation of temperature is variable and not of much help in diagnosis, as 63 per cent. show a temperature not over 100° F. Prophylaxis is important. In cases of nasopharyngeal inflammation accompanying the exanthemas, cleansing gargles and application of 20 per cent. argyrol should be used. Occurrence of earache in healthy children demands thorough examination of the nose and throat. In existing cases, paracentesis of the drum is very valuable when the membrane is bulging, or if it does not rupture early, or if the existing perforation gives insufficient drainage. A general anesthetic, preferably nitrous oxide gas, should be given in all cases. From 50 per cent. to 75 per cent. of cases if treated early can be aborted by rest in bed, free purgation, establishing good drainage, syringing with hot boric acid solution every two hours, and the application of cold to the mastoid by means of a Leiter's coil. This treatment may be kept up for from twenty-four to forty-eight hours. If there is no marked improvement in forty-eight hours, operation is necessary.

Coli Infection of the Urinary Tract in Childhood.—N. Percy Marsh (*Brit. Jour. Child. Dis.*, 1913, x, 385) points out that the colon bacillus is usually the cause of cystitis and pyelitis in childhood. Many other organisms such as streptococci, gonococci, staphylococci, etc., occasionally are causal factors. Escherich found the bacillus coli in 58 of a series of 60 cases. Jeffreys reports 67 coli cases out of 121. The difficulty in infants with this condition is in gathering sufficient urine to make a diagnosis, the case often being diagnosed marasmus or tuberculosis. While there is much disagreement on the mode of entry into the urinary tract by the colon bacillus, the fact that 90 per cent. to 95 per cent. of cases occur in girls suggests a direct infection through rectal contamination. The habit of wiping with the diaper from behind forward makes this easy. Another method of infection is from the bowel to the kidney, direct, and many cases do follow ileocolitis, intestinal ulceration, and long-continued constipation. Infection through the blood-stream is another theory. Clinically four conditions are recognized: Bacilluria, the bacilli being found in the mucous clouds formed on standing. Cystitis, in which the urine contains motile organisms and pus cells, and there are dysuria, increased frequency, and slight fever. Pyelitis, in which the constitutional disturbance is greater, with often rigor, shivering, and high, remittent temperature. Lastly, pyelonephritis with severe general symptoms, pronounced wasting, and tube-casts and albumin in the urine besides the bacilli. In infancy the onset is usually sudden, often assuming a remittent type, like enteric, later on. Squint, head-retraction, and drowsiness may simulate meningitis, and local symptoms may be absent altogether. The urine is usually acid, shows a mucous sheen, and has an unpleasant fishy odor. General edema is often one of the

general symptoms. In chronic forms in older children malnutrition is continued, the local symptoms are usually absent, and there is a slight febrile disturbance. The prognosis is variable, the acute cases clearing in one to several weeks, and a considerable number becoming chronic. The condition is rarely fatal. The two chief points in treatment are to ensure a copious secretion of urine, and to render the urine alkaline. The best drug is citrate of potash, 5 to 20 grains every three hours. Bicarborate of sodium or potassium or sodium citrate may also be used. Urinary antiseptics are used in acute cases, but not in chronic forms. Urotropin being decomposed only in acid urine it is applicable only to chronic cases in which the urine is kept acid. Autogenous vaccines have so far shown little if any result but should be tried as a last resort.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Induced Labor.—The induction of labor by pituitrin was reported by POULIOT and VAYSSIERS (*Bull. de la Soc. d'Obstét. de Paris*, June, 1912). The first dose was 1 c.c., repeated if required, and always given hypodermically. The cases comprised 2 of premature rupture of the membranes, 1 maternal syphilis with retention of a macerated fetus, 3 cases of slight pelvic contraction, and 1 of repeated hemorrhage at about five months. In contraction of the pelvis, the remedy seemed efficient in 2 cases, and useless in 1. When the membranes had ruptured prematurely, labor developed after pituitrin was injected. In a syphilitic patient, pituitrin had no effect. Where the uterus acted, it did so promptly with frequent and intense pain. The normal rhythm was maintained, and the uterus did not show signs of tetanus. Both mothers and children did well in these cases.

The place which induced labor should have in the treatment of contracted pelvis, is discussed by HOFMEIER (*Montasschr. f. Geburts. u. Gynäk.*, Band xxxvi, Festnumer, 1912). In 8000 labors, the induction of labor was practised in 71 cases—68 multiparæ and 3 primiparæ. In the primiparous cases he can give no reason for the induction of labor; 2 of them did well; in the third the child was lost; 16 of these were delivered with true conjugate from 6.5 cm. to 7.5; 43 with true conjugate between 7.5 and 8.5 cm.; and 12 cases where the true conjugate was greater than 8.5 cm. In 68 multiparæ operations were performed on 51 patients. The operation was repeated seventeen times, and in some cases three times upon one patient; 10 children were lost, 14 per cent., and in the first week after labor two others died, but not as the result of labor. This fetal mortality is greatly

lower than that which pertains in contracted pelvis when pregnancy is allowed to go on indefinitely. In regard to primiparæ, he does not believe that labor should be induced after the thirty-sixth week, nor where the true conjugate is less than 7.5 cm. In regard to the results for the mothers, in 71 cases there was no death, while the puerperal period was complicated by morbidity in 17 per cent. Hofmeier concludes from his experience that better results are obtained for mother and child if elective section at the beginning of labor is substituted for the induction of labor. He cites the case of a patient who, after repeated unfortunate and very difficult confinements, had induced labor with the birth of a living child, and who at the next pregnancy requested delivery by section, because it was a much simpler and shorter operation. This he believes will be the attitude of the patients in the future.

Brodhead (*Amer. Jour. Obstet.*, May, 1912) reports 139 induced labors with the modified Champetier de Ribes bag. Of these 75 were private, and 64 hospital or out-door patients. There were 48 primiparæ and 91 multiparæ; 75 were at or beyond full term, 53 between eight and nine months, 8 between seven and seven and one-half months, and 3 between six and six and one-half months. The cervix was first dilated by the finger or a steel dilator, and the bag rolled up into as small a bulk as possible was passed into the cervix and slowly filled with 1 per cent. lysol or salt solution. The stem was then clamped and tied. Bags No. 2 and No. 3 were used most frequently. In 4 of these cases, the membranes had ruptured, and, in 6, the membranes were accidently ruptured during manipulation. The length of labor varied in primiparæ from two hours and fifty minutes to seventy-nine hours and fifty-two minutes, the average being twenty-two hours and nine minutes. In multiparæ, the average duration of labor was fifteen hours and fifty-two minutes. Labor terminated spontaneously in 49 per cent.; with low forceps in 21 per cent.; with medium forceps in 11 per cent.; with high forceps in 3 per cent. Version was employed in 10 per cent., breech extraction in 3 per cent., craniotomy in 1 per cent., Cesarean section in 1 per cent.; and 1 patient, or 1 per cent. of all, died undelivered. Presentation of the child was changed in 7 cases, or 5 per cent., but in only 1 of these was the final result of labor altered.

Bagger-Jörgensen (*Monatsschr. f. Geburts. u. Gynäk.*, 1912, Band xxxvi, Heft 1) states that the opposition to the induction of labor for contracted pelves is usually based upon the fetal mortality. It has been his practice not to induce labor if the true conjugate was less than 8.5 cm.; thus, in 6400 labors, the operation was performed in 29 cases, among 100 cases of contracted pelves. From the thirty-fifth to the thirty-eighth week was the time chosen, with but 3 exceptions, 1 in the thirty-fourth week and 2 in the thirty-seventh week. In the majority, the bougie was used to excite labor pains, and in one patient it was necessary to introduce the bougie fourteen times before labor developed. The pains occurred in from fifteen minutes to eight days, usually in sixty hours after the first bougie was inserted. On account of the delay occasioned by this method, in the last 4 patients labor was induced by rupturing the membranes. Pains developed within thirty-two hours afterward, and the actual duration of labor was reduced

to thirteen hours. The birth was spontaneous. Where bougies were used labor lasted twenty-one hours; 63.4 per cent. of the children were born spontaneously. There was no maternal mortality, but 3 of the children died during labor—a primary mortality of 10 per cent. In one of these cases the cord prolapsed; in one case the bougie wounded the placenta, causing hemorrhage; and in one case the child died from asphyxia. The best time, in his opinion, for the operation, is the thirty-fifth week, and among his cases 90 per cent. of the children were discharged from hospital with the mothers living. During the first year of life among these children, the mortality was 8 per cent., or during the first two years, in all, 12 per cent.

UDACTA (*Rev. de Medicina y. Cirurgia Practicas*, October 14 and 28, 1912) publishes 2 cases reported at the Spanish Gynecological Society, where pituitrin was used in the treatment of uterine hemorrhage. The first patient was two months pregnant, having hemorrhage with clots and pieces of substances which apparently were placenta. On the third day after the first visit she had a hemorrhage, for which a hypodermic injection of pituitrin was given. Pain developed with the expulsion of a quantity of blood from the uterus, and about three-quarters of an hour later a blood clot and mass of placenta. The patient's symptoms speedily subsided and she made a complete recovery without further treatment. In the second case reported, the placenta was retained, and before proceeding to manual delivery pituitrin was given hypodermically. This caused the uterus to act and the placenta was expelled. The Society discussed the paper, and Botin reported 4 cases, in 3 of which the result was prompt and satisfactory, while in the fourth case pituitrin failed to produce uterine contractions. In the discussion, Botin spoke of the difficulty of removing the pituitary gland in the living animal. The interference required is so extensive that it is difficult to isolate the effect of the operation from the results produced by the ablation of the gland. A recent method by which the gland is removed through the orbit produces less traumatism and may improve the results. The action of pituitrin on the uterine muscle is in the beginning of its effect tetanic. This is followed by contractions like those of normal labor. Smaller doses are not efficient, and produce somewhat of the tetanic effect. The patient quickly becomes accustomed to its use, so that injections after the first, act with progressively less effect. With this in view, it is wise to reserve pituitrin for a decided emergency where immediate uterine contraction is essential. As it seems to enhance the normal action of the uterus, it can be used for inertia, and may obviate the necessity for forceps delivery. Others in discussion found that secondary relaxation of the uterus might produce hemorrhage. To avoid this, it seems best to use repeated injections. It is essential that the exact cause of delayed labor should be made out, as if pituitrin were used where an insurmountable obstacle to parturition was present, the results would, of course, be disastrous.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Female Labor and Gynecological Diseases.—A paper of considerable sociological interest has recently been published by HIRSCH (*Monat. f. Geb. u. Gyn.*, 1913, xxxviii, Ergzhft., 198), drawing attention to the steady increase in the proportion of women who are engaged in some regular occupation outside their homes, as a result of which they are constantly subjected to conditions more or less inimical to health, which in former times were practically unknown. The demands made upon the female organism by the bearing and rearing of children remain unchanged, however, and thus, Hirsch believes, arise in many instances pathologic conditions which, taken in the aggregate, are becoming of the greatest social as well as individual significance. Thus, work done constantly in a sitting posture causes pressure on the lower abdominal organs, resulting in inhibition of circulation and impaired digestive activity. Long standing, as is required in certain occupations, leads to increased intra-abdominal pressure, hernia, prolapse, and venous congestion in the lower extremities. Work in a more or less bent over posture often results in spinal curvatures, hernia, prolapse, possibly also renal and vesical disorders. In many industries, women are brought into constant contact with injurious substances, such as atmospheric impurities, dust, noxious gases, metallic or other poisons, bacteria, etc. The importance of these conditions from the gynecologist's point of view lies primarily in the fact that the genital organs, perhaps more than any others in the female body, are affected by any impairment of general constitutional tone, and deleterious influences are therefore apt to show their effects first in this sphere. With regard to specific industries, Hirsch has found that laundresses, seamstresses, textile workers, and clerks are especially prone to anemia and chlorosis, conditions which are often the direct precursors of tuberculosis, with all its serious effects upon pregnancy and labor. The records of the large Leipzig "Krankenkasse" show that abortion occurs about 7 times as frequently in working as in non-working women, premature labor 6 times, and various accidents of pregnancy (such as placenta prævia, hyperemesis, hemorrhage, extra-uterine gestation, etc.) about 3 times as frequently in the former as in the latter class. In certain industries, also, such as pottery manufacture, printing, straw hat bleaching, glass making, and in some textile branches, lead salts are employed, and it has been found that women employed in these trades are especially prone to premature labors and still births. This condition is apparently due to a toxic influence upon the maternal organism; not only does the lead pass through the placenta as has been proved by its presence in fetal organs, but it can be demonstrated in the mother's milk, and may thus lead to poisoning of infants born

alive. Similar conditions are found to a greater or less extent among women employed in all sorts of metal industries. In many occupations, such as copper working, dyeing, the manufacture of carpets, artificial flowers, toys, glassware, etc., chronic arsenic poisoning occurs, often entirely unsuspected, and gives rise to stubborn, deep ulcers on the genitalia; somewhat similar pathologic lesions are seen in women subjected to the influence of mercury, as in chemical works, the manufacture of mirrors, etc. In spinning and weaving establishments young women and girls are employed in large numbers, this work often resulting in stunted or deformed growth. In tobacco factories, in which a particularly large proportion of the workers are women, menstrual anomalies, cervical catarrh, and metritis are abnormally common. It has been shown statistically that women employed in all these industries have a higher percentage of sickness, and also a higher death rate, than do men of the same age employed in the same occupations, and numerous other forms of work exert likewise more or less specific effects upon the health of their female employees. Hirsch emphasizes the fact that this is a field of investigation which has as yet barely been entered upon, but which must in the near future receive thorough scientific consideration. Deleterious influences, such as have been spoken of, menacing a large and ever-increasing proportion of the female population, are of the utmost gravity, and require, in his opinion, the institution of energetic measures on the part of the state.

Menstrual Fever in Pulmonary Tuberculosis.—Weise (*Beitr. z. Klinik d. Tuberculose*, 1913, xxvi, 336), has made careful temperature measurements every two hours during the day over periods of several months, using as subjects 500 tuberculous women under sanitarium treatment, all of whom gave a positive tuberculin reaction, and most of whom had demonstrable tubercle bacilli in the sputum. He found a *premenstrual rise* of temperature in 201 cases (40 per cent.); in some instances this seemed to be distinctly associated with an aggravation of the patient's symptoms, in others, however, it appeared to be purely psychic. Fever *during* the period was present in 68 cases (13.6 per cent.). Although in a majority of these, the rise of temperature was slight, in a few it was quite marked, and was accompanied by severe constitutional symptoms. In 12 cases (2.4 per cent.) the temperature was normal before and during menstruation, but was elevated in the first few days *after* the termination of the period. In all these patients, however, the rise was slight, and of apparently little significance. There were 58 cases (11.6 per cent.), on the other hand, in which the temperature had been for some time above normal, but *fell* with onset of menstruation. In some instances, this fall was noticed only during one period, in others the fever did not recur. Weise thinks that this phenomenon may possibly be due to a favorable influence exerted on the pulmonary condition by the general hyperemia associated with menstruation. In the remaining 161 cases (32.2 per cent.) there was no noticeable change in the temperature before, during, or after the menstrual period. It would appear from these observations, therefore, that there is no *typical* form of thermic disturbance associated with menstruation in tuberculous subjects, but Weise does believe that the menstrual period on such women is a particularly critical

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time, during which they should be very careful to avoid the slighest exposure to cold, over-exertion, or other upsetting influences. He thinks moreover, that if in any woman a regular rise of temperature occurs at each menstrual period, the suspicion should be aroused of the possible existence of a tuberculous focus somewhere in the body, most probably in the lungs.

DISEASES OF THE LARYNX AND CONTIGUOUS STRUCTURES

UNDER THE CHARGE OF

J. SOLIS-COHEN, M.D.,

OF PHILADELPHIA.

Fracture of the Base of the Cranium as a Cause of Paralysis of the Palate, the Larynx, and the Shoulder.—SIEBENMANN (*Annales des Maladies de l'Oreille, du Lar., du Nez, et du Pharynx*, January, 1913) states that fracture of the base of the cranium may involve the nerves which supply the soft palate and the larynx, and likewise the accessory nerve which innervates the muscles of the shoulder. There may even be a lesion of the hypoglossal nerve as indicated by paralysis of the tongue. The lesion is usually due to a blow on the head which produces a fracture involving the region of the jugular foramen, and directed most frequently toward the sella turcica, and sometimes toward the pyramid.

Paraffin Injections into Paralyzed Vocal Cords.—BRUNINGS (*Annales des Maladies de l'Oreille, du Lar., du Nez, et du Phar.*, January, 1913) reports eight cases of vocal failure due to paralysis of the recurrent nerve, treated by the injection of paraffin into the paralyzed vocal cord. The injection is made by the direct method, and the paraffine must not be too hard.

On the Treatment of Vegetant Tuberculous Laryngitis.—CANESTRO (*Annales des Maladies de l'Oreille, du Lar., du Nez, et du Pharynx*, March 3, 1913), utilizing the necrosing action and slow cauterization of neutral quinia hydrochlorate, employed this drug in a typical case of vegetant tuberculosis laryngitis, and obtained transformation of this lesion into an infiltrated ulceration of good aspect, much more apt to succumb to the successful action of the usual remedies

The Anesthesia for Bronchoscopy.—EPHRAIM (*Annales des Maiadies de l'Oreille, du Lar., du Nez, et du Phar.*, January, 1913) replaces cocaine anesthesia for the larynx with a solution of 20 per cent. alypin, of which one part is mixed with three parts of adrenalin solution, 1 to 1000. For anesthesia of the trachea and the bronchi Ephraim uses a solution of the double salt of quinine and urea in the strength of 1

per cent. only, which produces a rapid and sufficient anesthesia, permitting not only the introduction of the tube but endobronchic intervention also. This solution is perfectly innocuous, and may be employed without any dread.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF
MILTON J. ROSENAU, M.D.,
PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.,
AND
MARK W. RICHARDSON, M.D.,
SECRETARY OF THE MASSACHUSETTS STATE BOARD OF HEALTH.

Roaches.—J. FIBIGER (*Berl. klin. Woch.*, February 17, 1913, No. 7, p. 289) has shown that roaches may become infested with a round worm, a new species of the genus *spiroptera*. When these infested roaches are eaten by rats (*Mus decumanus*), a cancerous-like growth develops in the stomach of the rats, presumably due to the irritating presence of these worms. The egg of the worm is passed in the feces of the rat, and the life cycle is completed by the roaches eating the eggs. Fibiger found tumors in only 11 out of 1144 rats caught in Copenhagen. On the other hand, out of 61 rats caught in the location of a sugar refinery, he found the worms in the stomach of 40, and pathological changes in the nature of a carcinomatous overgrowth in 18. Attention is drawn to the relation between this endemicity of the affection in rats and the supposed endemicity of cancer in man. The tumor-like overgrowth in the stomach of the rat is of the squamous epithelial type. Metastases sometimes occur. The rats cannot be infected by feeding them with the eggs of the worm; they must ingest the larvæ which occurs in the infested roach. Attention is drawn to a number of other investigators who have noted a relation between parasites, such as trichinæ, bilharzia, and flukes with human cancer. HERMS and NELSON (*Am. Jour. of Pub. Health*, September, 1913, iii, No. 9, p. 929), also LONGFELLOW (*Am. Jour. of Pub. Health*, January, 1913, iii, No. 1, p. 58), have shown the possibility of the conveyance of typhoid bacilli and other infections by means of the roach. When we consider that roaches feed upon all kinds of breadstuffs, milk and its products, meat, clothing, cooked and raw foods; that they migrate from one apartment to another, following water and drain pipes; that they come from cellar and sickroom to living rooms and bedrooms; and that they overrun pantries, kitchens, and storerooms, opportunity is evidently offered to drag infection mechanically from one place to another. The roach is, therefore, under the suspicion of being a sanitary menace.

Ozone.—E. O. JORDAN and A. J. CARLSON (*Jour. Am. Med. Assoc.*, September 27, 1913), studied the bactericidal, physiologic and deodor-

izing action of ozone, and W. A. Sawyer, Helen L. Beckwith, and Esther Skolfield (*Jour. Am. Med. Assoc.*, September 27, 1913) studied the alleged purification of air by the ozone machine. These two very important articles agree in their conclusions, to wit, that although some bacteria, especially if in a moist condition, may be killed by ozone, the amount necessary for this bactericidial action is so great as to affect injuriously human beings. As a disinfectant, formaldehyde is much more efficient. Ozone may mask odors, but the deleterious action of the ozone on the respiratory tract is of greater moment than the odor itself. The ozone machine should not, therefore, be allowed in schools, offices, or other places in which people remain for considerable periods of time. The machines conceal faults of ventilation rather than correct them.

Beriberi in the Amazon Valley not Due to Polished Rice.—Lovelace (*Amer. Jour. Tropical Diseases and Preventive Medicine*, August, 1913, i, No. 2, p. 140) reports the prevalence of a polyneuritis which is both clinically and anatomically indistinguishable from beriberi of the Orient. This disease is not associated with a rice diet and it is not due to the absence of any of the recognized food elements. It occurs in well-fed, non-rice-eating young adults, and presents a mortality of 15 to 20 per cent. Clinically there are two types, first, the cardiovascular type, in which circulatory symptoms, tachycardia, dyspnea, edema predominate; second, the paralytic type, in which paralysis of the various muscles with areas of abnormal sensation is the characteristic feature. Very often these two types occur together. Lovelace reviews the work of Fraser and Stanton, Strong and Eijkman, all of whom have shown that a diet of polished rice will cause polyneuritis. He accepts their conclusions but points to polished rice as only one etiological factor. His conclusions are: (1) Among the 963 cases of beriberi to which reference is made, were many in which the factors of defective diet and of a rice diet could be positively and definitely excluded. This is in line with the reports of many observes in many parts of the world. (2) The experiments of Fraser and Stanton, confirmed by other workers, are conclusive to the effect that the beriberi symptom-complex may be induced by a diet of polished rice. (3) As a corollary from these two conclusions and considering the multiplicity and diverse characters of the agents that are known to cause multiple neuritis, it is highly probable that the term "beriberi" is one that has been used to cover not a single disease, but a group of diseases, more or less indistinguishable clinically. (4) The question of the etiology of beriberi cannot yet be regarded as settled.

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ORIGINAL ARTICLES TO APPEAR IN THE JANUARY ISSUE, 1914

Differentiation of the Diseases Included under Chronic Arthritis.
LEWELLYS F. BARKER, M.D., Professor of Medicine in Johns Hopkins University, Baltimore.

Tuberculosis of the Breast.
JOHN B. DEAVER, M.D., Professor of the Practice of Surgery in the University of Pennsylvania, Philadelphia.

The Association of Uterine Growths with Goitre: Typical and Atypical Exophthalmic Goitre.
HENRY L. ELSNER, M.D., Professor of Medicine in Syracuse University, Syracuse, N. Y.

Factors Which May be Concerned in Causing Hypertrophy of the Thyroid Gland, and the Effect of Excision of this Organ upon Other Ductless Glands.
WILLIAM STEWART HALSTED, M.D., Professor of Surgery in Johns Hopkins University, Baltimore.

Auricular Fibrillation; Clinical Observations on Pulse Deficit, Digitalis, and Blood Pressure.
WALTER B. JAMES, M.D., Professor of Clinical Medicine in the College of Physicians and Surgeons, Columbia University, and T. STUART HART, M.D., Assistant Professor of Clinical Medicine in the College of Physicians and Surgeons, Columbia University, New York.

Some Causes of Disappointment in Operations on Brain Tumors.
WILLIAM G. SPILLER, M.D., Professor of Neuropathology in the University of Pennsylvania, Philadelphia.

Can it be Proved from Clinical and Pathological Records that the Number of Cures of Cancer Will Be Greatly Increased by the Proper Excision in the Earliest Precancerous or Cancerous Stage of the Local Disease?
JOSEPH COLT BLOODGOOD, M.D., Associate Professor of Surgery in Johns Hopkins University, Baltimore.

Unusual Type of Acid Intoxication in Infants.
ISAAC A. ABT, M.D., Professor of Pediatrics in the Northwestern University Medical School, Chicago.

Bleeding in Typhoid Fever.
ROBERT D. RUDOLF, M.D. (Edin.), F.R.C.P., Professor of Therapeutics in the University of Toronto, Toronto, Canada.

The Mechanism of the Circulatory Failure in Diphtheria.
W. G. MacCALLUM, M.D., Professor of Pathology in the College of Physicians and Surgeons, Columbia University, New York.

Experience with Neosalvarsan at the Harlem Hospital.
HOWARD FOX, M.D., Consulting Dermatologist to the Harlem Hospital, New York.

ORIGINAL ARTICLES TO APPEAR IN THE FEBRUARY ISSUE, 1914

A Further Note on the Kinetic Theory of Graves' Disease.
GEORGE W. CRILE, M.D., Professor of Surgery in the Western Reserve University, Cleveland, Ohio.

The Diagnosis of the Postcecal Appendix.
EDWARD MARTIN, M.D., John Rhea Barton Professor of Surgery in the University of Pennsylvania, Philadelphia.

The Treatment of Pylorospasm in Infancy.
JOHN RUHRÄH, M.D., Professor of Diseases of Children in the College of Physicians and Surgeons, Baltimore.

Splenectomy for Splenomegaly (Gaucher Type).
JOHN F. ERDMANN, M.D., Professor of Surgery, and JOHN J. MOORHEAD, M.D., Adjunct Professor of Surgery in the New York Post-Graduate Medical School and Hospital, New York.

The Minute Changes Produced in Leukemic Tissues by Exposure to Röntgen Rays.
ALDRED SCOTT WARTHIN, PH.D., M.D., Professor of Pathology in the University of Michigan, Ann Arbor, Michigan.

The Etiology and Pathogenesis of Bronchiectasis.
C. P. HOWARD, M.D., Professor of Internal Medicine in the University of Iowa, Iowa City, Iowa.

On some of the Broader Issues of the Psychoanalytic Movement.
JAMES J. PUTNAM, M.D., Professor Emeritus in the Harvard Medical School, Boston.

Dental Sepsis: Its Relation to the System.
C. N. B. CAMAC, M.D., Assistant Professor of Clinical Medicine in the College of Physicians and Surgeons, Columbia University, New York.

Hypertension: A Report of Cases under Prolonged Observation, and a Protest Against Some Ideas.
MILTON J. LICHTY, M.D., Assistant Clinical Professor of Medicine in the Western Reserve University, Cleveland, Ohio.

Pneumonic Hemiplegias.
CHARLES F. WITHINGTON, M.D., Visiting Physician to the Boston City Hospital, Boston.

The Mechanism of Prostatic Retention.
EDWARD L. KEYES, JR., M.D., Clinical Professor of Surgery in the Cornell University Medical College, New York.

IMPORTANT ORIGINAL CONTRIBUTIONS WHICH WILL APPEAR DURING THE SUCCEEDING MONTHS

Fatal Gastro-intestinal Hemorrhage.
GEORGE E. ARMSTRONG, M.D., LL.D. (Queen's), D.Sc. (Liverpool), Professor of Surgery in McGill University, and EMMET J. MULLALLY, M.D., Demonstrator of Bacteriology in McGill University, Montreal, Canada.

Exclusion of the Pylorus.
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The Treatment of Malaria.
C. C. BASS, M.D., Assistant Professor of Clinical Medicine in Tulane University, New Orleans.

The Role of Induced Sweating in Therapeutics.

WALTER A. BASTEDO, M.D., Associate Professor of Pharmacology and Therapeutics, College of Physicians and Surgeons, Columbia University, New York.

Clinical Data on Stone in the Ureter.

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Hyaline Degeneration of the Islands of Langerhans in Non-diabetic Conditions.

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Syphilis of the Liver Imitating Cirrhosis.

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CHARLES F. CRAIG, M.D., Captain, Medical Corps, United States Army.

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The Gastric Disturbances of Old Age.

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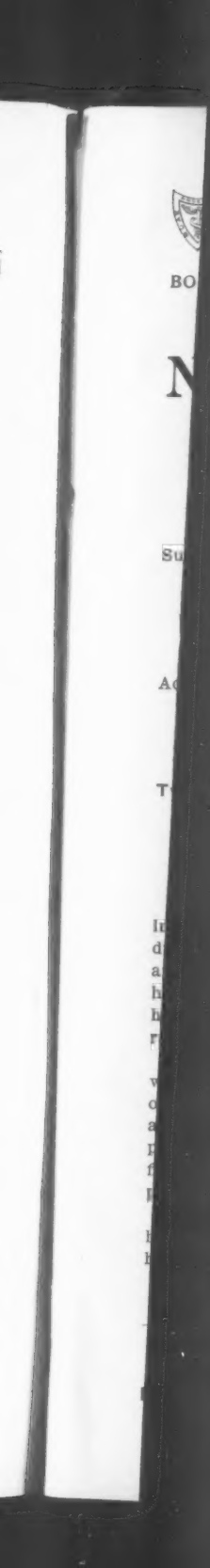

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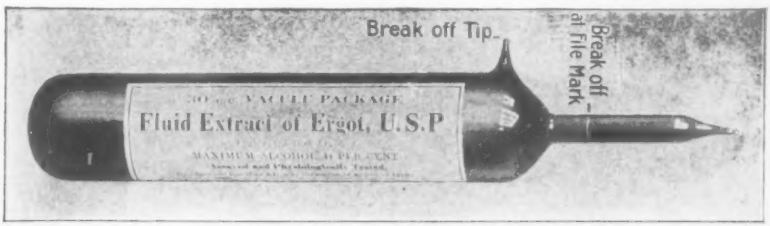

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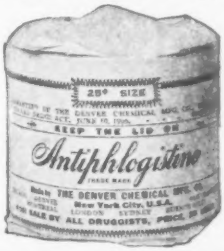

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